



CONSENSUS REPORT ON

REVITALISING CLINICAL RESEARCH IN SOUTH AFRICA

A STUDY ON CLINICAL RESEARCH AND
RELATED TRAINING IN SOUTH AFRICA



*Applying scientific thinking
in the service of society*

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The Academy of Science of South Africa [ASSAf] was inaugurated in May 1996 in the presence of then President Nelson Mandela, the patron of the launch of the Academy. It was formed in response to the need for an Academy of Science consonant with the dawn of democracy in South Africa: active in its mission of using science for the benefit of society, with a mandate encompassing all fields of scientific enquiry in a seamless way, and including in its ranks the full diversity of South Africa's distinguished scientists.

The Parliament of South Africa passed the Academy of Science of South Africa Act, Act 67 of 2001, and the Act came into operation on 15 May 2002. This has made ASSAf the official Academy of Science of South Africa, recognised by government and representing South Africa in the international community of science academies.

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LIST OF ACRONYMS

ABB	DESCRIPTION
AADI	African Academies Development Initiative
ACROSA	African Clinical Research Organisation of South Africa
ACU	Association of Commonwealth Universities
AIDS	Acquired Immunodeficiency Syndrome
ALLSA	Allergy Society of South Africa
AMCOST	African Ministerial Council on Science and Technology
ANU	Australian National University
APAST	ASEAN Plan of Action on Science and Technology
ASADI	African Science Academy Development Initiative
AsgiSA	Accelerated Shared Growth Initiative of South Africa
ASSAf	Academy of Science of South Africa
AU	African Union
BEE	Black Economic Empowerment
BScMed	Bachelor of Science in Medicine
CEIC	Ethics Committee for Clinical Investigation (Portugal)
CHED	Commission on Higher Education (Philippines)
CMSA	Colleges of Medicine of South Africa
CPAS	Centre for the Public Awareness of Science (Australia)
CRC	Clinical Research Consortium (UK)
CREST	Centre for Research in Science and Technology (South Africa)
CRO	Contract Research Organisations
CSIR	Council for Scientific and Industrial Research (South Africa)
CTC	Clinical Trials Committee
CWTS	Centre for Science and Technology Studies (Netherlands)
DACST	Department of Arts, Culture, Science and Technology (South Africa)
DEIC	Dutch East India Company

DES	Diethylstilboestrol
DFID	Department for International Development (Malawi)
DNE	Department of National Education (South Africa)
DoE	Department of Education (South Africa - now the Department of Higher Education and Training, DoHET)
DoH	Department of Health (South Africa)
DoHET	Department of Higher Education and Training
DST	Department of Science and Technology (South Africa)
DTI	Department of Trade and Industry (South Africa)
DUET	Database of Uncertainties about the Effects of Treatment
EDCTP	European and Developing Countries Clinical Trials Partnership
ENHR	Essential National Health Research
EU	European Union
FDA	US Federal Drug Administration
FEST	Foundation for Education, Science and Technology
FRD	Foundation for Research Development
GCP	Good Clinical Practice
GDP	Gross Domestic Product
GLP	Good Laboratory Practice
HG	Higher Grade
HIV	Human Immunodeficiency Virus
HPCSA	Health Professions Council of South Africa
HREC	Human Research Ethics Committee
HRT	Hormone Replacement Therapy
HSRC	Human Sciences Research Council (South Africa)
ICH-GCP	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice

IDRC	International Development and Research Centre (Malawi)
IIDMM	Institute of Infectious Diseases and Molecular Medicine
IP	Intellectual Property
IPAP	Industrial Policy Action Plan
IRENSA	International Research Ethics Network for Southern Africa
ISAP	Index of South African Periodicals in Sabinet
ISHReCA	Initiative to Strengthen Health Research Capacity in Africa
ISI	Institute of Scientific Information
MB ChB	Medicinæ Baccalaureus & Baccalaureus Chirurgiæ
MCC	Medicines Control Council (South Africa)
MD	Medicinæ Doctor
MDG	Millennium Development Goals
MHC	Major Histocompatibility Complex
MMed	Master of Science in Medicine
MOH	Ministry of Health (Singapore)
MRA	Medicines Regulatory Authority
MRC	Medical Research Council (South Africa)
MSTP	Medical Scientist Training Programme
MTT	Ministerial Task Team
NEPAD	New Partnership for Africa's Development
NGO	Non-Governmental Organisation
NHLS	National Health Laboratory Service (South Africa)
NHRC	National Health Research Committee
NHRD	National Health Research Database (South Africa)
NHREC	National Health Research Ethics Council
NHS	The National Health Service (UK)
NICD	National Institute for Communicable Diseases

NIH	National Institutes of Health (US)
NIPF	National Industrial Policy Framework
NIV	National Institute for Virology (South Africa)
NMRC	National Medical Research Council (Singapore)
NOL	No Objection Letter
NRF	National Research Foundation
OSCHR	Office for Strategic Coordination of Health Research
PCST	Public Communication of Science and Technology (South Africa)
PIASA	Pharmaceutical Industry Association of South Africa
PNHRS	Philippines National Health Research System
PRF	Poliomyelitis Research Foundation (South Africa)
PRU	Pneumoconiosis Research Unit
R&D	Research and development
RA	Regulatory Authority
RADUSA	Research and Development Uptake in South Africa
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAAPP	South African Association of Pharmaceutical Physicians
SAASTA	South African Agency for Science and Technology Advancement
SAAVI	South African AIDS Vaccine Initiative
Sabinet	South African Bibliographic Network
SACRA	South African Clinical Research Association
SAHRA	South African Health Products Regulatory Authority
SAIMR	South African Institute for Medical Research
SAK	SA Knowledgebase
SAMA	South African Medical Association
SAMJ	South African Medical Journal

SANDF	South African National Defence Force
SARETI	South African Research Ethics Initiative
SARIMA	Southern African Research and Innovation Management Association
SASCON	Southern African Science Communication Network
SCIFEST	Science Festival (South Africa)
SET	Science Education and Training (South Africa)
SG	Standard Grade
STEPS	Science, Technology and the Public Sphere (UK)
STI	Sexually Transmitted Infection
TB	Tuberculosis
TRAMED	Traditional Medicine
UCT	University of Cape Town
UKCRC	UK Clinical Research Collaboration
UKCRN	UK Clinical Research Network
UKECA	UK Ethics Committee Authority
UP-NIH	University of the Philippines – National Institutes of Health
USNA	United States National Academies
WITS	University of the Witwatersrand

FOREWORD



This report provides a review of the overall state of clinical research in South Africa. At the initiation of the study, the Study Panel's task was to review the existing scientific evidence regarding the current state of clinical research in South Africa. The review focused mainly on key clinical research issues as they were outlined in the brief. Some highlights of the findings include the fact that there has been too little research on the public understanding of science or of public perceptions of clinical trials in South Africa, and that there is currently no national plan to provide coordinated support for the education and

development of clinical researchers. More than half of the total expenditure on clinical research is by the private sector. Finally, since the public sector is playing too small role in this domain, it needs to become more actively engaged.

The study was initiated as a result of discussions with the Pharmaceutical Industry Association of South Africa (PIASA), which suggested that the Academy of Science of South Africa (ASSAf) should raise awareness of the value of good scientific clinical research to South Africa at top levels of government and academia. This also included raising awareness of the benefits of having clinical research units at universities, hospitals and research institutions in order to retain research scientists in the country, as part of the agenda of building a larger pool of researchers for the future. Proposers of the study were Prof. Wieland Gevers and Prof. Jimmy Volmink and former ASSAf staff member Ms Rudzani Ramaite. The ASSAf Council approved the study and approved the appointment of a 13-member Study Panel of experts.

The 13-member Study Panel, chaired by Prof. Bongani Mayosi, has completed the study and this report is the product of their work. The report has been peer

reviewed by one national and two international peers who recommended that the report be published. The ASSAf Council also has reviewed both the report and the reviewers' comments, and has approved the report for publication. The Council hopes that this report's recommendations and findings will lead to productive interventions, and the growth of high-quality clinical research in South Africa.

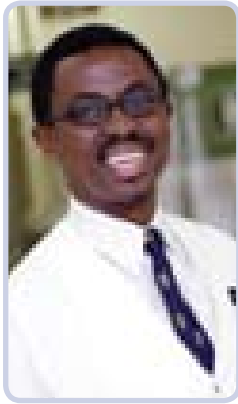
The report recognises that good clinical research is crucial for the development of the country, and thus recommends ways in which it can be revitalised and promoted. It proposes solutions to the challenges highlighted in the report. These recommendations are based on thorough analysis of the evidence obtained by the Study Panel. The report lists the recommendations in detail and further suggests which institutions and individuals can best facilitate the implementation of these recommendations. One of the key recommendations is that the South African Government should invest more money in clinical research.

The Council expresses its appreciation to Prof. Wieland Gevers and Prof Jimmy Volmink for proposing the study and thanks the chair of the Panel, Prof. Bongani Mayosi and all the Panel members for their participation and outstanding contributions to the development of the report. The support staff, Ms Phakamile Mngadi (Study Director), Dr Nthabiseng Taole (Project Manager) and Prof. Roseanne Diab (Executive Officer) are thanked for their contributions and assistance during the course of the study.

PROF. ROBIN CREWE

President: Academy of Science of South Africa

ACKNOWLEDGMENTS



This report is the joint work of a 13-member Study Panel appointed by the Council of the Academy of Science of South Africa (ASSAf). Each panelist has agreed to the specific formulation of the report and to its conclusions, findings and recommendations.

The Study Panel members were: Professor Bongani M Mayosi, MASSAf, University of Cape Town: Chairman; Professor Amaboo (Ames) Dhai, University of the Witwatersrand; Professor Peter Folb, MASSAf, Medical Research Council of South Africa; Professor Wieland Gevers, MASSAf, Academy of Science of South Africa (General Secretary); Professor Gregory D Hussey,

MASSAf, University of Cape Town; Ms Maureen Kirkman, Pharmaceutical Industry Association of South Africa; Dr Edith Nonhlanhla Madela-Mntla, Medical Research Council of South Africa; Professor Letticia Moja, University of the Free State; Professor Jagidesa (Jack) Moodley, University of KwaZulu-Natal; Professor Daniel Ncayiyana, *South African Medical Journal*; Professor William Pick, MASSAf, Council of Medical Schemes; Dr Nandi Siegfried, Medical Research Council of South Africa; and Professor Jimmy A Volmink, MASSAf, Stellenbosch University.

Dr Harriet Deacon served as the Study Researcher, and Ms Phakamile Mngadi was the ASSAf Project Officer for this study.

The Study Panel would like to acknowledge the following individuals for their assistance in compiling this report: Dr Richard Chawana, University of the Witwatersrand; Professor Peter Cleaton-Jones, University of the Witwatersrand; Dr Liesl Grobler, University of Cape Town; Ms Lee Louw, Stellenbosch University; Dr Percival Mahlati, National Department of Health of South Africa; Dr Philemon Mjwara, Department of Science and Technology of South Africa; and Ms Rudzani Ramaite (former ASSAf staff member). The Panel also wishes to express its gratitude to Professor Roseanne Diab (ASSAf Executive Officer),

Dr Xola Mati (ASSAf Chief Operations Officer), and Dr Nthabiseng Taole (ASSAf Project Manager) for their valuable support during the conduct of the study.

The Study Panel met on eight occasions from September 2007 to May 2009. Panel members were allocated different sections/chapters of the project and at these meetings the different sections were discussed. They deliberated on gaps/omissions, overlaps, possible contradictions/controversies, target audiences/ stakeholders for the different recommendations and aspects of the report. The draft sections were circulated to members prior to these meetings and a number of small sub-group meetings were also held. Internal reviews of the different sections/chapters were also undertaken by some members of the Panel, who were nominated (within the Panel) to do so.

Dr Richard Clark edited the pre-final draft report and Ms Beverlie Davies edited the final draft; the Panel appreciates their input. The three independent peer reviewers were: Professor Adesola Ogunniyi (Nigeria), Dr Mamphela Ramphele (South Africa), and Professor Sir David Weatherall (United Kingdom). The Panel wishes to thank them for their insightful comments that have enriched this report.

The Panel also acknowledges the financial support provided by the United States National Academies (USNA) through the African Science Academies Development Initiative (ASADI) programme, as well as funding provided by the South African National Department of Science and Technology.

PROF. BONGANI MAYOSI

Chairperson: Clinical Research and Related Training in South Africa

CONCISE BRIEF OF THE STUDY

1. What was the brief of the ASSAf Council to the Study Panel?

The brief of the Study Panel that was appointed by the Council of the Academy of Science of South Africa (ASSAf) was to examine and address the most relevant and reliable evidence on the key questions below, especially regarding clinical trials, and to make recommendations that were most appropriate and feasible, based on that evidence:

- (i) How to build a national culture in which clinical research is seen as essential and clinical trials are widely accepted and promoted as the most reliable basis for establishing the efficacy and safety of new therapies, procedures and approaches?
- (ii) How to equip and encourage clinicians-in-training to embrace clinical research and evidence-based practice as indispensable elements in delivering effective health care?
- (iii) How to improve the level of funding and execution of clinical research for investigator-driven clinical research, including clinical trials research?
- (iv) How to ensure that clinical research flourishes in South Africa under conditions that protect the rights and safety of individuals?
- (v) How can government, parastatal institutions, academia and industry interact more constructively in creating a favourable and enabling environment for clinical research to be conducted?

2. Why was the topic addressed by ASSAf and not by another body?

According to its Act, Act 67 of 2001, ASSAf is obliged to:

"Provide effective advice and facilitate appropriate action in relation to the collective needs, opportunities and challenges of all South Africans". The Academy may, "at the request of any person or on its own initiative, investigate matters of public interest concerning science and on the strength of the findings act in an opinion-forming and advisory manner".

ASSAf has influence as a high-level, independent and constructive body. This influence can be used more effectively in bringing about policy change to make a contribution in an interlocking area of national importance and opportunity that has resisted resolution and reform over many years, and caused considerable frustration in its participant sectors. ASSAf, through a panel of experts, could examine areas that would lead to significant improvements and influence government perceptions regarding the value of clinical research and related training to the South African economy and health system, by engaging with senior government officials in a number of ministries, e.g. the Presidency, Health, Education, Science and Technology, Finance, and Trade and Industry. Each of these departments has a vested interest in improving the health status of the nation and providing access to adequate, affordable health care in a framework of economic and social prosperity. It would be entirely feasible for ASSAf to examine identified special topics where further focused studies or workshops would be appropriate, including how funding would be sourced.

EXECUTIVE SUMMARY

Clinical research in a developing country like South Africa contributes to health care at all levels by identifying the causes of problems, facilitating diagnosis, improving the efficiency and effectiveness of care, and promoting good policy-making. It also supports the training of competent health professionals of all kinds, and contributes to global knowledge about locally, as well as generally, prevalent diseases in terms of prevention and treatment.

The key narrative of clinical research in South Africa over the last two decades has been that of a largely unplanned, but cumulative, disinvestment in publicly funded programmes, resulting from the withdrawal of the health departments of provincial governments from this sector (academic hospitals are now funded for service functions only), the absence of discounts for research tests from the business model of the National Health Laboratory Service (NHLS), chronic underfunding of the Medical Research Council (MRC) despite its obviously important mandate for maintaining and developing medical/clinical research capacity in the country, and the lack of funding streams to universities that might in principle have been applied to meet the overall shortfall in support.

These intersecting developments are a kind of 'elephant in the room', well known to all participants, but very poorly documented. Tertiary service units struggle to remain active in research, and to translate their expertise into improved health service. As a result, many clinical researchers have been left with no option but to turn to the pharmaceutical industry for the funding of those clinical trials in which the companies concerned have an interest, or to international donors who conduct large-scale, short-to medium-term, projects in South Africa, with local researchers drawn into international teams, often led by outsiders. The pharmaceutical investment is directed predominantly at the profitable areas of chronic diseases of lifestyle, mental illness and allergy, while most of the external donor funding is directed at the serious local HIV and TB pandemics. Local and international clinical conference activity has accordingly begun to reflect the agendas of donors and industry. There is

little likelihood that continuation of the present situation is compatible with rebuilding and sustaining solid research capacity in the clinical domain, nor can the ideal of well-coordinated state support for a health system, built on the 'intelligence' of good clinical research, ever be realised.

The serious decline in clinical research activity and capacity has prompted this study by ASSAf (<http://www.assaf.org.za>) in order to make recommendations on the overall revitalisation of clinical research in the country within the broad paradigm of essential national health research. An additional stimulus is the emphasis of government in its ten-year science and technology plan on the development of new medicines and other biologically useful agents ('farmer to pharma').

* * *

In **Chapter 1** we engage with the questions as to **what clinical research is, and why it is important**. The following working definition of clinical research has been adopted:

Clinical research is research primarily conducted with human participants (and on material derived from them, such as tissues, specimens and cognitive phenomena) during which investigators examine the mechanisms, causation, detection, progression and reversal of human disease.

Clinical research is important because it can improve health outcomes by establishing the effects of health care interventions, and because it promotes and facilitates best-possible health care practice. It is a crucial element in the education of health care workers and the effective provision of appropriate clinical services. Revitalising clinical research is thus in the national interest and requires efficient and supportive management and encouragement at all levels.

* * *

In **Chapter 2** we engage with the **history of scientific medicine in South Africa**, and briefly assess its achievements and limitations. Specifically, we examine the legacy of colonialism, racism and inequality in medical research, and ask

how this history has shaped the relationship between researchers, government, industry and the South African public.

From the beginning of the 20th century, medical researchers in South Africa began to develop a strong scientific base for clinical research in terms of personnel and infrastructure, conducting important investigations into a wide range of medical problems. The present burden of disease in South Africa is significantly linked to the country's history of racial and gender inequality, violence, oppression and enforced labour migration, and to some of the failures of post-apartheid independence. It is characterised by high levels of both communicable and non-communicable disease, particularly those that are related to poor working conditions and poverty, gender-based violence and injury. Because of the colonial context, clinical investigations (with some notable exceptions) were largely driven by the needs of the mining and agricultural industry, or focused on curative medicine in urban areas, and generally did not aim to improve the health of the population as whole.

Clinical research in the apartheid years was conducted by a cohort of investigators who were mainly white and male, within a system that provided racially unequal access to health care and research training. Institutional capacity to conduct clinical research was concentrated in a few historically white institutions. Some clinical research in the colonial and apartheid eras was racist and unethical, facilitated by an environment of racial inequality, discrimination and high status and wealth differentials under an oppressive state.

After 1994, significant strides were made in reorienting health care and medical research towards the needs of the majority at a policy level, but in practice the tangible benefits of this have been limited by reduced government support for medical research within the health care system, a weak education system, and poor management of existing resources within the health care system, in the face of serious new challenges such as HIV/AIDS and tuberculosis.

Accordingly we recommend that clinical research should be repositioned within a more democratic political and societal context, to build on the advantages of past investment while actively addressing the legacy of

colonialism. Clinical research should contribute to the improvement of the health of the nation by purposefully addressing the largest burdens of disease as empirically determined and consultatively agreed. The training and promotion of clinical researchers should seek to address racial and gender imbalances, and ensure that a strong intellectual leadership is built. The funding of clinical research should seek to develop strengths wherever these can best and most sustainably be built. Finally, clinical research should be based on strong ethical codes of conduct.

* * *

In **Chapter 3** we ask what shape a **national culture** supporting clinical research would have to take for it to be supportive of good clinical research, what its principal components would be, and to what extent present conditions fall short of these requirements. We believe a national culture supporting clinical research will accept the value of clinical research based on the principle that 'the proper study of humankind is humans themselves'; will understand that sustainable health care systems require guidance by a critical mass of clinicians experienced in research and the continuous training of new generations of research-informed clinical care-givers; will recognise the importance of investment in clinical research due to its complex and multi-dimensional nature; will enable an appropriate balance between risks and benefits in clinical research while ensuring ethical practice; will attain an appropriate balance between curiosity-driven and problem-directed research in addressing key health risks in society; will place a clear emphasis on public service and public benefit in the conduct of clinical research, will promote the protection and development of intellectual property; and will enhance public trust in, and understanding of, the role and contribution of research in society.

Accordingly we recommend raising the status of clinical research, both within the broader domain of scientific research and within government programmes funding science; creating a strong public service and benefit ethos based on better programmes promoting public engagement with clinical science and better risk-benefit analyses that inform prioritisation of clinical research

in the country; capacitating local ethics and regulatory bodies for clinical research; developing an interdisciplinary local scientific community through scientific publishing and coordinated promotion activities while encouraging links between laboratory-based and clinical research; enhancing specialist knowledge and competence that is internationally visible without reducing interdisciplinary communication among clinical researchers within South Africa; creating targeted educational programmes, funding, career-pathing and institutional support for the development of new clinical researchers in the country; increasing, and better coordinating, the funding of clinical research; and working towards a concerted and coordinated effort by government, industry and research institutions to promote and develop clinical research capacity at the highest level possible.

* * *

In **Chapter 4** we ask how fostering better **public engagement with science** can promote a national culture supporting clinical research. What do we know about public opinion concerning clinical research in South Africa, and what can we do to improve public understanding of, and trust in, clinical research?

We find that there has been too little research on the public understanding of science or on public perceptions of clinical trials in South Africa, that there is a legacy of distrust and ignorance in the relationship between research participants and clinical researchers because of the history of South Africa, and that mutually beneficial engagement between the public and clinical researchers has not been extensive enough in the past. Although South Africa is still an attractive location for clinical trials, and recruitment of subjects for clinical trials is still relatively easy in the country (due to a large treatment-naïve urban population that is experiencing high unemployment and has difficulty accessing expensive drugs), this may change unless attention is given to public perceptions through careful engagement.

We therefore recommend raising the profile of clinical research on the African continent, for example, in the African Science Communication Network and the Southern African Science Communication Network (SASCON), and

including clinical research as a further flagship research and development cluster for the 2011-15 *African Science and Technology Plan of Action*. We also suggest raising the profile of clinical research within South Africa, for example by broadening National Science Week to incorporate a National Health Research Week, and by establishing an ASSAf award for Promoting Public Engagement with Clinical Science.

We recommend that public engagement with science should be deepened, for example by funding qualitative and quantitative research about the public understanding of science, motivating for a National Research Foundation (NRF) Research Chair in Public Engagement with Science, ensuring that clinical research is included in the agenda, and by including public engagement with science in the NEPAD indicators for African science, technology and innovation.

We suggest reviewing the new curriculum statements in schools, making specific reference to therapeutic/clinical concepts based on an historical (longitudinal) approach in order to make useful connections between chemistry, human physiology (e.g. endocrinology as an internal 'drug-administering system'), mathematics literacy, ethics and economics.

We wish to ensure a more democratic engagement between the public and researchers, so that they share a common understanding of the operation and purpose of clinical research, for example by developing locally appropriate public communication guidelines and ethical protocols for researchers, engaging with public views about clinical research, including geopolitical issues as part of research preparation activities, and promoting rights access and education for trial participants.

Attention must be given to strengthening the capacity of health and science journalists to assist in accurately conveying the essence of clinical research approaches and findings to the public, and permitting the public airing of concerns.

* * *

In **Chapter 5** we examine the current mechanisms of **ethical oversight** of clinical research in South Africa, and ask how well these mechanisms are functioning, how ethical oversight mechanisms for clinical research function elsewhere, and how we can improve ethical oversight of clinical research in South Africa.

We conclude that research should be viewed as a social enterprise, i.e. a contract with society, whereby ethically conducted research will serve to assure society that individuals will not be harmed. The primary function of Research Ethics Committees (RECs) is the protection of research participants, including adequate scientific review for excellence and relevance. The laws governing the conduct of research in South Africa are generally adequate, as are the institutional provisions for ethics governance and regulation; the National Health Act has set the standards for ethics in research but implementation of these standards is far from being realised.

While legislative changes have resulted in increasing numbers of research projects requiring ethics review and approval, there has not been a parallel increase in support of REC functioning, resulting in often unnecessary delays (this is particularly problematic regarding multi-centre studies). Very few RECs are in a position to honour their obligations to monitor and provide oversight of the research they approve, despite the fact that the majority of REC members in South Africa are health scientists and clinicians and that RECs operate largely within university environments. The shift of clinical trial commissioning from academic institutions to the private sector has weakened the access of academic institutions to funding and their ability to develop research capacity, so that only a handful of core researchers are doing trials, and conduct too many trials concurrently.

We recommend that institutions and the Department of Health must both support RECs both from an administrative and review perspective. This must include post-approval responsibilities, including passive and active monitoring of approved research; the monitoring and evaluation of REC functioning; and making information about clinical research widely available.

The National Health Research Ethics Council should register and accredit RECs and expedite their ability to process applications. A system of expedited review for minimal risk research would result in a significant reduction in the overall turn-around time for study proposals. Institutions and RECs should collaborate to reduce duplication in ethics review within South Africa, and thus facilitate multi-centre studies.

Focused, ongoing educational programmes for existing and potential REC members on ethics protocol review, current and past ethics research discourse and debate, and ethics regulation are required to ensure competent, high-quality review, which itself should be subject to quality assurance at pre-determined intervals.

The ethics of publishing needs ongoing attention to avoid the problems of sponsor-driven content, and to ensure complete disclosure of conflicts of interest.

* * *

In **Chapter 6** we investigate what key problems in South African clinical research can be identified by an analysis of **published outputs**, and explore specific interventions that might best promote overall productivity of clinical research in terms of both quality and quantity.

We find that while South African scientific publishing represents a small fraction of world output, it comprises a large proportion of scientific research on the African continent. Clinical research has formed an important part of South Africa's scientific output, in terms of quality and quantity. Although the total number of clinical medicine journal articles has declined since 2003, nearly half of the fields in clinical research have recorded above-average field-normalised and journal-normalised citation rates for the period 2002 to 2006. The trend has been towards increased publication of clinical medicine journal articles in international journals, particularly in a wide variety of specialty journals. Although more female and black authors have been publishing than before, progress has been slow and the proportion of older authors has been rising.

We recommend that more high-quality clinical research should be published in local, especially multidisciplinary, journals, requiring specific steps such as fully recognising and rewarding publications in local journals of high quality. We also recommend increasing opportunities for local publication, for example by establishing vibrant supplements to existing journals and/or establishing a new, open access, multidisciplinary journal for clinical research, possibly as a 'daughter' of the existing flagship publication, the *South African Medical Journal*. A national society for clinical research should be established.

* * *

In **Chapter 7** we seek to address the declining size and increasing age of the **workforce** actively engaged in clinical research, and the paucity of effective training programmes and unattractive career-pathing in the clinical research sector.

We find that the clinical research force is ageing and has been steadily declining in numbers since the early 1990s. The combined burden of clinical teaching and training, health service, and research thus falls on a shrinking and ageing pool of academics in health science faculties. This means that there is limited capacity to increase the production of properly trained health care workers and to train and inspire a new generation of clinical researchers. Simultaneously, the situation has brought about an inability to cope with the increasing demands of clinical service imposed by the colliding epidemics of infectious disease (TB and HIV/AIDS) and non-communicable disease (heart disease and stroke).

There is currently no national plan to provide coordinated support for the training and development of clinical researchers, and grossly insufficient support for research professorships and training fellowships in the clinical research field. There is little incentive for clinicians to train in doctoral programmes, resulting in a very small number of the clinical professoriate having doctoral degrees.

We recognise that the National Human Resources Plan for Health that was launched by the national Department of Health (DoH) in 2006 emphasises

the general shortage of health professionals in South Africa, and consider that clinical research needs to be identified as a priority area for implementation. The Colleges of Medicine of South Africa (CMSA) has a policy forum on tertiary academic medicine and specialist training, which should support these aims. The DST's Ten-Year National Plan for Innovation aims to develop a knowledge-based economy in which the production and dissemination of knowledge leads to economic benefits and enriches all fields of human endeavour: clinical research should clearly be one of the most important focus areas in the Plan.

We recommend the creation of a national plan for research capacity development in the clinical sciences (a 'National Clinical Scholars' Programme') for undergraduate and postgraduate students, and for junior and senior faculty in clinical research, based partly on the idea of the PhD as the key driver for progress in this area, as part of the human capital generation project of the Department of Science and Technology's (DST's) Ten-Year National Plan for Innovation. This should be a publicly funded training programme for the production of the clinician research workforce from undergraduates with the necessary talent and aptitude (through student research fellowships), and from 20% of postgraduates (through clinical research fellowships). A target should be set for 500 PhDs to be produced in the clinical research field over the next 10 years, while 30 national research chairs should be earmarked for the clinical sciences.

The objectives of the proposed 'National Clinical Scholars' Programme' may be achieved through expansion of the intercalated research year model of selective training of motivated undergraduates in carefully planned curricula designed to establish a life-long interest in research, re-design of the MMed research component to enhance its effectiveness in research training and competence, and to serve as the basis for MD/PhD study, and stimulating PhD degrees for professional graduates by widening the necessary opportunities and support mechanisms, including use of modules and learning methodologies from BSc Med honours programmes. Provision should also be made for the purposeful training and career-pathing of non-clinical graduates who can become important partners in clinical research programmes.

We also propose the creation of a flexibly managed and supported clinical academic career track in all disciplines in the Academic Health Complexes under the Health Sciences Academic Development Programme of the DoH. A new cadre of clinical lectureships and clinical professorships needs to be established in all clinical disciplines to rejuvenate and expand the pool of clinical research trainers and academic clinicians in general. We suggest the promotion of training for biostatisticians and other supporting professions for clinical research at universities. We propose the incorporation of ethics into clinical research training and education. We ask for the establishment and funding of learnerships for graduates in the research facilities of large multinational and national companies, and suggest the development and support of a network of skilled mentors who can lead the development of young clinical researchers.

The establishment of large-scale research institutes dedicated to collaborative clinical research and innovation is a cost-effective and efficient way of developing high-level capacity at the cohort level, recognising as it does the integration of multiple skills and disciplines in order to address complex health problems and create new approaches to health promotion and treatment of prevalent and burdensome diseases.

We also ask for the creation of a 'National Clinical Research Coordinating Centre' at the MRC to link and coordinate clinical research centres and clinical trials programmes at universities, research councils, government and industry. Such a network (which would operate best if accorded a large measure of operational independence while retaining overall accountability) would foster collaborative research efforts, training programmes and research projects aimed at strengthening patient-orientated research. The Centre should seek to increase the participation of foundations, pharmaceutical companies, health insurance firms and the managed care industry in the clinical training enterprise.

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In **Chapter 8** we ask how much developing countries should be **spending** on medical and particularly clinical research. Specifically, we look at how

much the South African Government spends on research and development (R&D), and of this, how much is spent on medical, and specifically clinical, research. How are funding priorities determined? Through which institutions is government funding allocated? What are the other sources of funding?

We believe that 2% of the gross domestic product (GDP) of developing countries is a necessary minimum investment in indigenous science and technology development, with health research receiving at least 20% of that amount.

South Africa is spending more on R&D than before, but this is still less than 1% of GDP. The largest part is spent on engineering and technological sciences, and on the natural sciences (40% of total R&D expenditure; about 20% each), while expenditure on the health sciences is 15% of the total (about 0.15% of GDP). The government spends a large amount on services in the public health sector (about 10% of all state expenditure), but much too little of this money is spent on health research, which is also poorly coordinated and inadequately documented. Clinical trial expenditure by industry is not included in this figure. Most of the current funding for health research comes from donors outside the country and the pharmaceutical industry. More than half of the total expenditure on clinical research is done by the private (business) sector.

We encourage the DoH to enable the National Health Research Committee, or a similar body, to perform the key functions of creating an enabling environment to conduct research in South Africa; building better relationships between scientists and clinicians and between clinician-researchers and policy-makers; promoting clinical research in South Africa; communicating between the research community, National Treasury and the various national departments; ensuring that institutions provide technical and managerial support services to all their researchers; and improving regulatory procedures. A non-politicised *modus operandi* would provide the best results.

We believe there has to be more effective tracking and monitoring of funding streams for clinical research and substantially increased public funding of clinical research, applied in such a way that national health priorities are more

effectively addressed than is currently the case. The DoH should apportion 2% of its allocation to health research.

Regional clinical research centres/hubs should be established, each with clinical and preclinical expertise and facilities.

We believe that the policies and operational plans of various participants such as the DoH, and the Departments of Higher Education and Training, Science and Technology and Trade and Industry, the NHLS, the MRC and the provincial health departments should be more effectively coordinated, facilitated by the new Ministry of Coordination and Planning.

A 'National Joint Agreement' should be formed between universities and departments of health and education, which should systematically provide a 'research platform' alongside the clinical and teaching platforms of the Academic Health Complexes, as envisaged in the National Health Act of 2003.

* * *

In **Chapter 9** we look at the existing **institutional arrangements** for specific investments in clinical research in South Africa, and ask what kinds of interaction are needed between government, parastatal institutions, academia and industry to revitalise clinical research.

We believe South Africa could and should be recognised internationally as a centre of excellence for clinical trials that could attract more investment in trials. This would ensure retention of skilled scientists, sustain the ability of medical research facilities at universities or research institutions to continue to conduct basic research and novel medicinal research, and attract foreign direct investment to the benefit of the South African economy.

The present Medicines Control Council's (MCC's) Clinical Trials Committee performs a review function on all clinical trials. This process, which has improved recently after its legislated change into a Regulatory Authority (RA), is still experiencing serious problems, including approval delays, variation in reviewer quality and inadequate supervision of trials.

We recommend that the new RA should rigorously meet its newly set statutory requirements to ensure that any medicines used in the country are safe and effective. The authority should rely on sound ethics review.

An increase in the number of clinical trials conducted in South Africa (with recognition of South Africa as a 'centre of excellence' for conducting such studies) would require agreement on a reasonable time-to-approval for clinical trial applications (e.g. a reduction of approval time to less than eight weeks), efficient processing of all applications with clearly understood requirements, and regular dialogue between the new South African Health (products) Regulatory Authority and all role-players. The regulatory process for approval of clinical trials could be expedited in a number of ways. For example, after auditing, standardisation and accreditation of RECs by the National Health Research Ethics Council (the NHREC), a system could be envisaged in which RECs approve or reject clinical trials and simply notify the RA of the clinical trials concerned. In addition, once an application to conduct a clinical trial had been submitted to the RA, the company or institution could proceed with the trial if a no objection letter is received from the RA within a specified time frame. Where application has been made for the registration of an identical product under another trade name for strategic marketing reasons, only one 'Master Dossier' could be submitted and reviewed. There could be recognition of prior approvals in selected countries. To make these measures work, the RA could require local RECs to conduct ongoing audits of studies they have approved.

The implementation of the Intellectual Property Rights for Publicly Financed R&D Act, *Act 51 of 2008*, needs to be carefully aligned with the ethical-regulatory framework to maximise benefits in both sectors and to prevent them from impeding the proper functioning of the other.

* * *

In **Chapter 10** we ask what kinds of interventions have been used successfully **elsewhere in the world** to address the kinds of challenges South African clinical research is facing.

We find that although health research, and especially clinical research, is acknowledged as indispensable for improving health, promoting equity and stimulating development, it tends inexplicably to be neglected in sub-Saharan Africa in terms of planning, status and funding. Much attention has been paid to promoting clinical research in the North, in the face of challenges similar to those afflicting the South, so it is possible that solutions already found elsewhere could also be applied here. These include maintaining the supply of skilled clinical researchers, improving facilities for clinical research, increasing funding and strengthening translational research.

We believe that government commitment and partnership is needed to revitalise clinical research. The government of Singapore, for example, invests in clinical research to translate the biomedical research emanating from its highly competitive research institutes into clinical applications; to inculcate a knowledge- and evidence-based approach to health care; and to retain the highest level of medical talent in the public hospitals.

There must be a closely cooperative and mutually trusting relationship between researchers and health policy-makers and implementers. The National Health Service (NHS) in the UK, the Department of Health and Social Services in the US (through the National Institutes of Health [NIH]), and the Ministry of Health in Singapore all engage in partnership with the research community through numerous channels and at numerous levels to support clinical research.

Efforts should be targeted at building indigenous research capacity. Singapore has a definite career path for clinician-researchers, and promotes and rewards performance in clinical research through special awards for research excellence.

High-profile advocates are required to promote clinical research. One example of an advocacy body is the Initiative to Strengthen Health Research Capacity in Africa (ISHReCA), bringing together health researchers in Africa to promote the creation of self-sustaining pools of excellence capable of initiating and carrying out high-quality health research in Africa.

Better strategic planning and coordination for health research is required. An example of such an initiative is the Health Research Capacity Strengthening Initiative partnerships in Kenya and Malawi.

* * *

In **Chapter 11**, the final chapter, we list what we consider to be the **barriers to revitalising clinical research in South Africa**:

1. Inadequate public engagement with clinical research

- Government does not promote clinical research sufficiently in the public domain;
- Researchers do not engage sufficiently with issues of importance to research participants and policy-makers.

2. Lack of research planning, regulation and coordination

- Lack of a coordinated national plan to balance excellence on the world stage (i.e. quality and impact) with relevance to local problems;
- An inefficient regulatory framework for clinical trials and registration of new medicines is hindering the conduct of innovative clinical trials.

3. Inadequate capacity for clinical research (human resources and infrastructure)

- Poor teaching of and matriculation rates in mathematics and science in schools;
- Lack of appropriately trained clinical scientists and career structure to support them (i.e. 'frozen demographics' of ageing white male clinical scientists with too few young, black and woman researchers);
- Lack of appropriate facilities and infrastructure (i.e. virtual absence of dedicated clinical research centres).

4. Lack of adequate and appropriate funding

- Inadequate funding for clinical trials and other types of clinical research (e.g. the MRC project grant has an upper limit of R130 000 p.a.);
- The cost-recovery regimen of the provincial departments of health and the National Health Laboratory Service (NHLS) prohibits investigator-driven, non-industry clinical research in academic health complexes.

5. Absence of monitoring and evaluation

- No monitoring of adherence to standards and performance of individual researchers, academic institutions, research councils, government departments, the health industry and other funders of research.

We now list the proposed synergistic solutions:

1. National Strategic Planning, Regulation and Coordination of Clinical Research:

- We propose the formation of a 'South African Clinical Research Coordinating Centre' at the MRC, with maximum possible operational independence, to serve as an advocacy group and a partnership of organisations working to establish South Africa as a world leader in clinical research by harnessing the power of all stakeholders, including universities, government departments, the NHLS, the health industry and research councils;
- The proposed Coordinating Centre should engage with a re-energised National Health Research Committee on how optimal planning, regulation and coordination of clinical research may be achieved, in consultation with the Departments of Health, Higher Education, Science and Technology, and Trade and Industry;
- The proposed Coordinating Centre should interact with the newly established National Planning Unit in the Presidency on the planning needs of clinical and health research;

- The proposed Coordinating Centre should seek to play an advisory role to the proposed Medicines Regulatory Authority (MRA; successor to the Medicines Control Council) and the National Ethics Committee in order to deal with the regulatory environment and ethical oversight for clinical trials and health research in general;
- The proposed Coordinating Centre should ensure the alignment of the clinical and health research effort with the principles of Essential National Health Research and other policies of the government;
- The proposed Coordination Centre should oversee the implementation of the Intellectual Property Rights Act and ensure that it results in a proper alignment between the ethical-regulatory regimens and the protection of new intellectual property in the clinical domain.

2. Human and Infrastructural Capacity:

- A 'National Clinical Scholars' Programme as part of the Ten-Year Plan for Innovation of the DST;
- A target of 500 PhDs to be produced in clinical health sciences over the next ten years as part of the plan by the DST to increase the graduation rate of PhDs in general to 6 000 per year between 2008 and 2018, plus a target of 150 postdoctoral fellows per annum working in South African clinical research environments;
- A target of 30 research chairs in clinical research areas to help tackle the 'Farmer to Pharma' Grand Challenge and other strategic areas.

3. The creation of clinical research centres and research institutes as national hubs in the academic health complexes and other sites:

- Develop a National Joint Agreement between universities and the Departments of Health, Education and Science and Technology in order to provide a 'research platform' alongside the clinical and teaching platforms in the academic health complexes and other sites;
- Create a 'National Clinical Research Training Coordinating Initiative' to link and coordinate clinical research training at universities,

research councils, government and industry. This initiative will serve as a warehouse of education and training opportunities (i.e. projects, funding, courses, degrees), and a meeting place for supervisors and potential students at a national level;

- Establish large-scale research institutes where opportunities for high-level collaborative clinical studies exist, and a critical mass of principal investigators, postdoctoral fellows, graduate students and research assistants can be assembled.
- Establish attractive, high-capacity training programmes for undergraduate and postgraduate students in the clinical health sciences, as well as for junior faculty in clinical research, as part of the human capital generation project of the DST's Ten-Year Plan for Innovation;
- Fund learnerships for graduates in the research facilities of large multinational companies;
- Foster a clinical-plus-research academic career track (lectureships and professorships) in all clinical disciplines in South African institutions;
- Develop and support a network of skilled mentors who can lead the development of young clinical researchers.

4. National Funding Scheme for Clinical and Health Research:

- Raise the national R&D budget to 2% of the GDP, of which 20% should be allocated to health research (DST);
- Implement the Mexico declaration commitment by the national DoH to spend 2% of the national health budget on research and development, and amend the Research and Development Tax Incentives Policy to encourage innovative R&D in South Africa by removing the specific exclusion of clinical trials (DTI);
- Incentivise the health care industry (pharmaceuticals and private hospitals) to spend 2% of its turnover on R&D (pharmaceutical manufacturers and others);

- Follow up on the recently implemented Clinical Training Enhancement Initiative with a well-aligned approach to clinical research training.

5. Monitoring and Evaluation of the Clinical and Health Research Enterprise:

- Evaluation of the performance of the clinical research enterprise in South Africa, possibly under the aegis of the Academy of Science of South Africa, by reviewing the implementation of the recommendations of this report at five-yearly intervals;
- Monitoring by the National Health Research Committee of the efficiency of the research spend of the MRC and other statutory bodies entrusted with publicly funded health research;
- Monitoring by the new Monitoring and Evaluation Unit in the Presidency of government's ability to meet the target of spending 2% of GDP on R&D, and 2% of the health budget on health research.

CHAPTER 1: INTRODUCTION:

CLINICAL RESEARCH IS THE KEY TO BETTER HEALTH CARE

In this chapter, we engage with the following questions:

1. What is clinical research?
2. Why is it important?

INTRODUCTION

The term **clinical research** means different things to different people. Broadly speaking, it can be taken to be that part of **scientific enquiry which is directly aimed at improving patient care, by studying affected patients themselves**. Formulating a more precise definition of clinical research, however, offers greater challenges. Clinical researchers comprise individuals from different disciplines, who work in diverse settings and employ a variety of tools and instruments in seeking answers to the wide array of questions that arise in clinical practice. As a result of this diversity, the way in which they characterise their activity often varies markedly, rendering elusive a universally acceptable definition of clinical research.

In this chapter, we begin with an overview of the **dominant paradigms** within which clinical research can be understood. Thereafter, we present the most common operational definitions of clinical research currently in use and specify the definition ultimately adopted by the Panel; this section also draws attention to the intimate linkages between clinical research and other types of medical or health care research. Next, we examine the central role of clinical trials in the evaluation of the effects of treatments, and introduce systematic reviews as a relatively new form of scientific endeavour aimed at weighing existing clinical evidence. Finally, we offer a brief discussion of the importance of the clinical research enterprise within the South African context.

PERSPECTIVES ON CLINICAL RESEARCH

Three **major paradigms** exist within which clinical research can be understood. These will, for the sake of convenience, be referred to as 'epidemiological', 'pharmaceutical' and 'translational'.

From an epidemiological perspective, clinical research is seen as the application of the methods and techniques of epidemiology (a population science) to clinical decision-making. The main focus is thus on the fact that groups of patients or healthy people are studied in order to make health predictions about individuals. The term '**clinical epidemiology**' has been coined to distinguish this research domain from classical epidemiology, which focuses on guiding decisions at the aggregate public health level. As shown in the box below, clinical researchers (also known as clinical epidemiologists) study a wide selection of issues that are pertinent to patient care.

RESEARCH INTERESTS OF CLINICAL EPIDEMIOLOGISTS (Fletcher and Fletcher, 2005)

Abnormality	Is this patient sick or well?
Diagnosis	How accurate is this test?
Frequency	How often does this disease occur?
Risk	What factors increase the risk of this disease?
Prognosis	What are the consequences of this disease?
Treatment	Does treatment change the course of this disease?
Prevention	Does early intervention keep this disease from occurring?
Cause	What conditions lead to the disease?

The classification of clinical research provided by Grimes and Schultz (2002) offers further insight into the epidemiological paradigm (see Figure 1.1). In this approach, clinical research can be divided into **experimental and observational studies**, depending on whether or not the investigator allocates the exposure (treatment). Experimental studies are further subdivided into **randomised and non-randomised trials**, and observational studies into **analytical or descriptive categories**. Analytical studies incorporate a comparison (control) group, whereas descriptive studies do not. Furthermore, within analytical studies, **cohort studies** follow people forward from exposure to outcome, contrasting with **case-control studies** in which individuals are traced backwards from outcome to exposure. **Cross-sectional studies** in turn are snapshots of exposures and outcomes within a group at one instant in time. Finally, **descriptive studies** such as case series lack a comparison group and therefore cannot examine associations, although they can be important for generating hypotheses.

Clinical researchers are able to choose from any of the above study designs. As each design offers specific strengths and limitations, the choice should be determined by the research question being examined.

A second, considerably narrower perspective on clinical research is encountered in the biopharmaceutical industry where clinical research is seen as part of the **drug development process**, comprising distinct **preclinical and clinical phases**. Preclinical research involves laboratory screening for promising chemical compounds, as well as research on laboratory animals to assess the toxicity and biological activity of these entities. A small percentage of the compounds so tested proceed to the stage of clinical research, with four phases of human experimentation. **Phase I trials** concentrate on dose determination, safety and pharmacokinetics, and typically involve small numbers (<100) of human volunteers. **Phase II** trials are also small-scale, and are often placebo-controlled studies of efficacy and safety conducted among patients suffering from a particular target disease. **Phase III** trials are fully powered in the statistical sense, and are usually randomised studies in which the efficacy of a new drug is assessed in relation to placebo or another active drug as comparator. Finally, **Phase IV trials** consist of post-marketing surveillance studies that can provide useful information on drug adverse effects, but are not infrequently initiated with the purpose of bringing the new drug to the attention of a large number of clinicians, often on a geographic or regional basis.

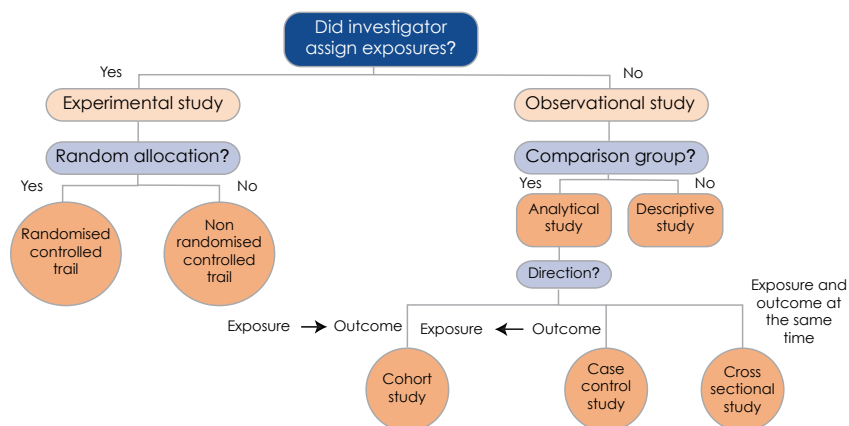


Figure 1.1: Algorithm for classification of types of clinical research

Translational science is the third lens through which clinical research may be viewed. The establishment and growth of laboratory-based biomedical science from the 20th century onwards contributed greatly to a better understanding of human biology and disease mechanisms, and this in turn has led to many important medical breakthroughs, such as the discovery of antibiotics, cures for many nutritional disorders, eradication of smallpox and treatments for diabetes and HIV/AIDS. Concern has, however, often been expressed about the fact that many basic science discoveries have not (yet) resulted in direct benefits to patients. Organisations such as the US National Institutes of Health (NIH) have strongly promoted and supported 'translational research' in order to bridge this gap between basic science and clinical application.

The pathway of discovery within a translational science paradigm typically begins at 'the bench' where scientists study the mechanisms of disease at a molecular or cellular level, with subsequent progress to the clinical level ('the bedside') where studies are conducted to determine whether findings in animal models apply to human disease states. Proof-of-concept evidence has to be generated prior to potential therapies being tested in clinical trials. Much

of this research tends to emphasise 'mechanistic studies' aimed at furthering the understanding of physiological or pathological processes in humans, rather than evaluating the effects of rational interventions. Understanding these underlying processes is nevertheless very important for accelerating the development of novel approaches to treatment, improving the safety profile of existing interventions and advancing new diagnostic methods.

It is well understood, however, that new discoveries are not always initiated at the bench. Observations by astute clinicians of variations in disease processes in different patients may generate important hypotheses for testing in the laboratory, which in turn can spur important new innovations. Translational research can thus be regarded as being a bi-directional ('bench-to-bedside and back-to-the-bench') process in which basic scientists and clinical researchers are engaged in a symbiotic relationship.

In summary, three main perspectives on clinical research are currently identifiable. For some, clinical research is the application of epidemiological methods in the search for valid answers to questions regarding diagnosis, prevention, therapy, prognosis, aetiology and other issues relevant to patient care. Others view clinical research as experimental research aimed at establishing the risks and benefits associated with new pharmaceutical products. A third group regards clinical research as a scientific activity directed at testing or generating hypotheses about disease mechanisms, with the ultimate aim of accelerating the translation of basic science discoveries to useful clinical applications. It is obvious that the three perspectives are mutually interdependent.

CLINICAL RESEARCH DEFINED

There is a lack of agreement among clinicians and scientists on the type and scope of activities that constitute clinical research. Various scientific and medical bodies have, nonetheless, sought to formulate operational definitions of clinical research mainly for the purposes of tracking research activity or documenting funding flows in research. In this section, we highlight the most widely used of these definitions and clarify the working definition adopted by the Panel.

Clinical research is defined by the US National Institutes of Health as health-related research conducted on human beings or on specimens collected from specific patients, but not on human tissues, where the identity of the people from whom the cells or tissues are derived is unknown (NIH Directors' Panel Clinical Research Report, 1997). The NIH Directors' Panel Clinical Research Report of 1997 grouped clinical research into three parts:

- a. Patient-oriented research:** research conducted with human participants (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with humans. This area of research includes:
 - Mechanisms of human disease;
 - Therapeutic interventions;
 - Clinical trials;
 - Development of new technologies;
- b. Epidemiologic and behavioural studies;**
- c. Outcomes research and health services research** (NIH Directors' Panel Clinical Research Report, 1997).

This definition excludes *in vitro* studies that utilise human tissues but do not deal directly with patients (i.e. where it not necessary to know the identity of the patients from whom the cells or tissues under study have been taken).

A similar broad-based definition has been adopted by the Medical Research Council in the UK, which views clinical research as human research involving at least one of the following categories (<http://www.mrc.ac.za>):

- a. Human participation:** studies that require face-to-face contact with patients and/or healthy human participants and may involve the use of patient records, e.g. a clinical trial;
- b. Record-based studies:** studies that require access to personal data on health or lifestyle without involving face-to-face contact with any people,

e.g. epidemiological studies, health economic studies, public health interventions, health services research and meta-analyses;

- c. Clinical samples:** studies that involve laboratory studies on human material which are specifically designed to understand or treat a disease/disorder. Basic biomedical research of remote relevance to a disease/disorder, e.g. use of immortalised human cell lines in model biological systems is excluded;
- d. Technology development for clinical use:** development or adaptation of technologies for diagnosis or therapy, e.g. instrument development for diagnostic or surgical use; development of new techniques for clinical use, such as photodynamic therapy.

The UK Medical Research Council has also offered a conceptual model for understanding the linkages between clinical research and other forms of medical research (Figure 1.2) (Sutton, 2004). Within this framework, the term 'medical research' is seen to encompass a broad range of activities aimed at improving or maintaining human health, and comprises both basic and clinical research. Clinical research involves research on human participants, while 'basic research' refers to underpinning research from areas such as animal studies, psychology, epidemiology, statistics, economics, physics, chemistry, and so forth. Furthermore, it can be observed that experimental medicine and population science do not exclusively fall into the domain of clinical research, but cross the boundary between clinical and basic research. Finally, translational research is depicted as a two-way bridge from basic science to clinical application and health care delivery.

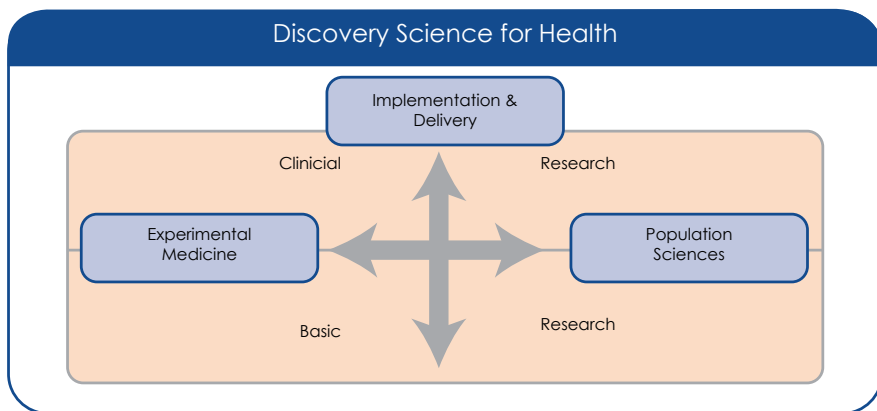


Figure 1.2: A conceptual UK model for understanding the linkages between clinical research and other forms of health research

Given the considerable blurring of traditional boundaries between basic and applied science, or experimental and observational research, it is not surprising that definitions of clinical research adopted by most professional bodies have tended to be inclusive. This Panel has followed this trend and decided upon the following working definition:

Clinical research is research primarily conducted with human participants (and on material derived from them, such as tissues, specimens and cognitive phenomena) during which investigators examine mechanisms, causation, detection, progression and reversal of human disease.

CLINICAL TRIALS – THE CORNERSTONE OF CLINICAL RESEARCH

As the ultimate goal of clinical research is to improve health outcomes, it stands to reason that establishing the effects of clinical interventions and strategies would be its central concern. In the past, judgments about what treatments do or do not work were based on theories about how the body functions, and anecdotal clinical reports concerning treatment outcomes. While these approaches remain important, there is greater awareness today of their many limitations.

Theoretical models of disease mechanisms, derived from laboratory research on cells, animals or human tissues, may be imperfect, incorrect or lack applicability to humans. Consequently, application of knowledge derived from theoretical constructs does not automatically translate into effective treatment, and in some instances may result in harm. Clinical experience, unlike preclinical research, offers the advantage of being able to directly observe health-related events in humans. Unless careful steps are taken to reduce bias in the course of making these observations, however, clinicians may reach dangerously false conclusions regarding treatment effects. It is now widely accepted that clinical trials provide the most reliable evidence for establishing the efficacy and safety of therapies, procedures and strategies in health care.

This section accordingly explains what a clinical trial is and discusses the reasons why this particular study design has come to assume favoured status within clinical research.

Clinical trials are organised experiments in which outcomes in participants who are assigned active treatment are compared with those receiving an alternative active treatment, a placebo (inactive treatment) or no treatment. Clinical trials, however, vary in the rigour of their design. Not all trials use a concurrent control group, and where they do, participants may or may not be randomly allocated to comparison groups. Furthermore, blinding of participants, providers and those assessing treatment outcomes to the group to which participants were assigned, while desirable, is not always undertaken and may in some instances not be feasible.

Historically, the first known controlled clinical trial appears to have been the study of scurvy treatments conducted by James Lind in 1753 (see text box below). It took two centuries for the approach now known as the randomised controlled trial (RCT) to be introduced. The relevant landmark study, an evaluation of streptomycin in the treatment of pulmonary tuberculosis, represented a significant step forward in the scientific evaluation of health care. The RCT has since been widely embraced as the gold standard for assessing the effects of new treatments. Before setting forth some theoretical

arguments for the superiority of RCTs within this context, we will briefly illustrate (with examples from practice) the dangers inherent in drawing conclusions about treatment effects from alternative types of evidence.

An important early example of experimental research in clinical medicine

In the mid-18th century, long before the discovery of vitamin C, the Scottish naval surgeon, James Lind, conducted a controlled study among 12 sailors at sea in search of a cure for the then deadly disease of scurvy. Taking care to select patients who were at a similar stage of the disease, on a similar diet and accommodated in similar conditions, he separated them into pairs in order to test six different treatments in use at the time: cider, sea water, vinegar, dilute sulphuric acid, oranges and lemons and a concoction of nutmeg, mustard and garlic. Lind reported: "The consequence was, that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them, being at the end of six days fit for duty." This work was remarkable for its role in the elimination of scurvy from the British Royal Navy, sadly however, only fifty years later, due to delay in implementing the findings of this important study.

The tale of bloodletting can next be considered as a medical therapy widely adopted without proper evidence. During the 1832 cholera epidemic in France, treatment consisted of bloodletting by surgical venesection and the application of leeches. The practice was based on the theory that the redness, heat and swelling seen as local inflammation were due to an excess of blood which led to a build-up of pressure. It seemed logical that the removal of blood would lessen the pressure, thus mitigating the inflammation. On this basis, the practice of bloodletting was used in Europe for over a hundred years, including by such luminaries as Sir William Osler, before it was finally accepted that the practice was harmful and should be discontinued.

Such instances of dangerous clinical practice are not limited to the pre-scientific era. Take for example the exposure of more than three million pregnant women to the 'wonder drug,' diethylstilboestrol (DES) from the 1950s to the early 1970s. Supported by promising findings in animal studies and anecdotal clinical evidence in humans, the hormone was widely promoted for preventing miscarriages and other complications of pregnancy. Twenty years later, many of the daughters of women given DES developed a rare vaginal cancer (adenocarcinoma), as well as other cancers and primary infertility, while many of their sons developed testicular malformations. This tragedy was all the more significant given the knowledge that an RCT published as far back as 1953 had demonstrated that DES had no effect on pregnancy complications compared with placebo. Had these findings been taken seriously, the disaster may well have been averted.

A more recent example is the routine prophylactic use of class I anti-arrhythmic drugs in patients suffering a heart attack. Based on the finding that these drugs could suppress abnormal heart rhythms in the laboratory, they were introduced into clinical practice in the belief that they would reduce mortality in the early period after a heart attack when such abnormalities are most common. Contrary to expectation, when RCTs were eventually carried out to test this hypothesis, the risk of death was found to be significantly higher among those on anti-arrhythmic treatment, compared with those receiving placebo.

When the effects of treatment are inferred from the findings of observational clinical research rather than from systematic clinical experience, bias in the selection of participants and confounding factors can still result in false conclusions. The following examples illustrate why caution is required in interpreting the results of observational research. Recently, prospective observational studies found that people with higher intakes of vitamin E, vitamin C and other antioxidants had reduced rates of cardiovascular disease and cancer, compared with those with lower intakes. In contrast, subsequent RCTs demonstrated that risks were either similar in these groups or higher in those taking antioxidant supplements. Similarly, the notion, based on findings

of observational research that the use of hormone replacement therapy (HRT) resulted in lower risks of heart attacks and strokes in post-menopausal women, was dispelled by a recent large RCT finding that was exactly the opposite.

The question may reasonably be asked: what makes the RCT so special that its findings should be regarded as being more trustworthy than those of other types of studies? There are key features of RCTs which underpin their special status as dependable sources of evidence:

First, RCTs provide **direct evidence** for an effect of a particular treatment in human populations. Such proof is more reliable than indirect evidence derived from animal models which may or may not be applicable in humans; such evidence remains valid even when the reasons for the treatment effect are not fully understood.

Second, RCTs are **prospective studies**, which means that the exposure (treatment) is known to precede the disease outcome; a prerequisite for inference about causality. By contrast, assurance of a correct temporal relationship between cause and effect is lacking in retrospective or cross-sectional clinical studies.

Third, in RCTs the exposure (treatment) is **under the control of the investigator**, i.e. the investigator assigns the treatment. This is different from observational studies where the investigator relies on historical information about whether or not participants have been exposed, which is more susceptible to bias.

Fourth, RCTs employ **comparative information (controls)**. Control groups limit bias in the evaluation of treatment by addressing two issues: a) people may recover from illness without any treatment, and b) natural fluctuations in the course of a disease may make it seem that a treatment is helping or hurting when in reality it may be having no effect. Comparing the experience of those receiving treatment with that of people not on treatment therefore helps reduce the likelihood of falsely attributing a particular clinical outcome to the effect of treatment. The importance of

this principle has long been recognised as can be seen in the quotation from Claude Bernard, the famous 19th century physiologist: "Comparative experience is a prerequisite for experimental and scientific medicine, otherwise the physician may walk at random and become the sport of a thousand illusions" (Tröhler, 2000).

Finally, and perhaps the most powerful reason of all: RCTs can **ensure the comparison of 'like with like'**. An important consideration in the evaluation of the effects of treatment is that participants in comparison groups should be sufficiently similar at baseline so that any differences in outcomes can be confidently attributed to treatment rather than to other factors. **Randomisation**, which ensures that participants have an equal chance of being allocated to intervention or control groups, is the only available method that can reduce bias resulting from unequal distribution of known or unknown factors than can influence clinical outcomes.

BEYOND CLINICAL TRIALS

The value of clinical research studies as guides to clinical practice (or future research) depend on the extent to which three important conditions are fulfilled: a) all relevant research that has addressed a particular question is available for assessment; b) an appraisal of the validity of each study has been undertaken; and c) a scientific synthesis has been conducted that provides insight into apparent conflicts in study findings or, where appropriate, an overall summary of the findings.

This idea is contained in the now famous statement by the epidemiologist and physician Archie Cochrane in 1979: "It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials" (Cochrane, 1979).

A scientific methodology for conducting research syntheses (known as the '**systematic review**') has been developed in response to this challenge, as well as in respect of mounting proof of the shortcomings of traditional methods of review, including individual RCTs. Systematic reviews are considered to

be more reliable than traditional (informal) reviews or expert group review for weighing existing evidence, and therefore for informing health care decisions.

Systematic reviews are increasingly regarded as the most authoritative source of evidence on the efficacy of preventive, therapeutic and rehabilitative interventions in clinical medicine. They are widely promoted by the international Cochrane Collaboration, a not-for-profit, independent organisation (<http://www.cochrane.org>), dedicated to making up-to-date and reliable information about the effects of health care readily available worldwide. The organisation is also strongly endorsed by the World Health Organisation.

FINDINGS

1. The following working definition of clinical research has been adopted for the purpose of this study:

Clinical research is research primarily conducted with human participants (and on material derived from them, such as tissues, specimens and cognitive phenomena) during which investigators examine mechanisms, causation, detection, progression and reversal of human disease.

2. Clinical research is important because it can improve health outcomes by establishing the effects of health care interventions and because it promotes and facilitates best-possible health care practice.
3. Clinical research is a crucial element in the education of health care workers and the effective provision of appropriate clinical services.
4. Revitalising clinical research is thus in the national interest and requires efficient and supportive management and encouragement at all levels.

REFERENCES FOR CHAPTER 1

Cochrane, A. L. 1979. 1931-1971: A critical review with particular reference to the medical profession. In: *Medicines for the Year 2000*. London: Office of Health Economic. pp. 1-11.

Grimes, D. A. and Schulz, K. F. 2002. An overview of clinical research: the lay of the land. *The Lancet*. p 359.

Fletcher, R. H. and Fletcher, S. W. 2005. *Clinical Epidemiology: The Essentials*, Fourth edition. Baltimore: Lippincott Williams & Wilkins.

National Institutes of Health (NIH). 1997. Directors' Panel Clinical Research Report 1997. Available at: <http://www.nih.gov/news/crp/97report/execsum.htm>.

South African Medical Research Council. Available at: <http://www.mrc.ac.za>.

Sutton, G. 2004. James Lind aboard Salisbury. *The James Lind Library*. Available at: <http://www.jameslindlibrary.org>.

The Cochrane Collaboration. Available at: <http://www.cochrane.org>.

Tröhler, U. 2000. *To improve the evidence of medicine: The 18th century British origins of a critical approach*. Edinburgh: Royal College of Physicians.

CHAPTER 2:

HISTORICAL STRENGTHS AND WEAKNESSES OF CLINICAL
RESEARCH IN SOUTH AFRICA

In this chapter, we engage with the following questions:

1. What is the history of scientific medicine in South Africa, its achievements and limitations? Specifically, what is the legacy of colonialism, racism and inequality in medical research?
2. How has this history shaped the relationship between researchers, government, industry and the South African public?

THE BIRTH OF SCIENTIFIC MEDICINE

The emergence of **scientific medicine** in Europe during the *Renaissance* was characterised by greater interest in gathering and documenting observable, replicable, experimental data on diseases and their treatment, and to explain the mechanisms underlying what was observed. Although there were some ancient medical experiments and investigations, and the development of long-standing **folk or traditional health care practices** would necessarily have depended on various forms of trial and error, these mostly remained undocumented and unchallenged. The formal experimental method in clinical research is generally assumed to have arisen in Europe during the *Renaissance* and the following Enlightenment era. Lind's small clinical trial in the 1750s – discussed in Chapter 1 – was part of an experimental tradition in Western medicine that emerged through physiological studies in the sixteenth century and was subsequently applied to the testing of medical therapies (Sutton, 2004).

SOUTH AFRICAN CONTRIBUTIONS TO THE DEVELOPMENT OF SCIENTIFIC THINKING IN EUROPE

Science in Britain's American, Asian and African colonies influenced metropolitan science both by expanding the available natural history data for European scientists and by providing a channel for new kinds of knowledge, for example about indigenous medicines (Tröhler, 2000). Cook (2007) has suggested that the search for objective evidence based on investigations, characteristic of the new scientific thinking in Europe, grew out of the needs of commerce rather than the shortcomings of religion. In particular, one of the key drivers for the scientific revolution in 17th and 18th century Europe was the requirement for information of organisations like the Dutch East India Company (DEIC). The Cape was established as an outpost of the DEIC, ensuring that its ships revictualled *en route* to the East. There were a number of visitors to the Cape in the 18th century who took medical information back to Europe, on which basis some plants indigenous to the Cape (*buchu* and *aloe*) were exported and included in European *pharmacopoeia* (Deacon, 2004). Even before there was a strong local cadre of scientists, South Africa was contributing in this indirect way to the development of scientific thinking in Europe.

Close connections were maintained with Europe through immigration, visits and the training of doctors, and some therapies based on early clinical trials came to be more widely used in South Africa. The folk method of smallpox inoculation (variolation), for example, was tested in the Netherlands in 1756 by de Monchy. He and other Rotterdam doctors conducted a trial on 32 people, including De Monchy's own daughter (Haagsche, 1757). De Monchy subsequently recommended variolation to the Cape Governor and it was implemented before the epidemic of 1767 (Burrows, 1958). In 1798, Jenner published experimental results (using children) showing the safety and effectiveness of cowpox vaccination against smallpox (Booth, 1993). This information was brought to the Cape by a British doctor on his way to India two years later, and when a Portuguese ship later brought slaves vaccinated with cowpox into the port, local trials using arm-to-arm vaccination to test its safety and non-infectiousness were done on slave children. Local doctors testified to the beneficial consequences of vaccination observed in Europe. The Batavian government at the Cape set up a Vaccination Committee to provide free voluntary vaccination for the public (Burrows, 1958), and in 1805 smallpox vaccination was taken into the Cape hinterland by the German doctor Lichtenstein (Sandler, 1974).

The establishment of **research-oriented universities** and **specialised clinics** during the late 19th century in Europe and later in the US encouraged the detailed study of specific diseases. Scientific medicine depended on new ways of seeing disease (e.g. microscopes), and new mathematical concepts such as sampling and randomisation. By the mid-19th century, better microscopes enabled German histologists to show that all living organisms were made out of cells, and helped Virchow to develop a new concept of disease based on disturbances of the cellular structure of the human body (Booth, 1993). Western doctors began to see mathematics and physics as essential to their experimental work, providing statistical tools as well as measuring instruments to assess physiological phenomena. Increasingly, it was scientific investigation that differentiated 'medical school' (orthodox) medicine from other forms of health care.

In the 19th century, South African-based doctors, lacking a critical mass of researchers and a local medical school, were somewhat slower to develop institutionalised medical research than their European counterparts. The absolute number of doctors was relatively low in the Cape, and there were only 45 licensed doctors in 1807-8 (in a settler population of just under 30 000), increasing to 629 in 1904 (in a settler population of around 580 000) (Deacon, 2004). The polymath Atherstone's successful experiment with anaesthesia in 1847 was perhaps the most famous Cape medical experiment of the time. Because it was one of many similar experiments elsewhere in that decade, however, it did not substantially change the practice of anaesthesia (Burrows, 1958). A. Smith, the first Superintendent of the South African Museum in 1825, was a regular correspondent of Darwin (Cluver and Smith, 1988); J. Herschel mapped the Southern sky from Cape Town before returning to Britain to become the President of the Royal Society, and other local scientists also directly and indirectly influenced scientific thinking in Europe.

Science offered new ways of testing old remedies, for example the use of a decoction of willow-tops for fevers, common as a folk remedy among Khoisan and Dutch settlers at the Cape (Volmink, 2008), but local trials were few. Mackrill, Barry and Atherstone conducted experiments on folk, settler and

indigenous plant remedies (Price, 1959). In the 1830s, a Cape Town surgeon, S. Bailey, reportedly used “a ... [Xhosa] medicine ... made of herbs from the Eastern Cape” which “he put ... great faith in” (*Quarterly Bulletin of the SA Library*, 1969). Even so, experimentation with local medicinal plants was not very widespread at the Cape. When district surgeons were asked to send in accounts of indigenous plants and their medicinal use to government in 1829, very few responded (Deacon, 2004). The results of this kind of scattered experimentation were not systematically shared among the profession, which lacked a local medical school or strong professional organisations. South African doctors tended to distance themselves from indigenous and folk healers who used indigenous plants (Deacon, 2004).

A great deal of **European colonial science** was focused on supporting the economic and political objectives of empire and its local representatives. Although doctors were not simply agents of empire, there was a close relationship between the medical profession and the colonial state from the 19th century onwards. The medical profession thus focused initially on the plant sciences and meteorology in the development of cash crops, mapping, surveying and anthropology in the maintenance of colonial rule, and entomology and clinical medicine in the control of disease that affected black workers and white colonists (Palladino and Worboys, 1993). British imperial policy after 1918 aimed to “create research and technical assistance agencies in individual territories where they could be guided by and best serve local economic and political interests” (Palladino and Worboys, 1993). By the 1950s, South African research interests were strongly influenced by the growing international scientific research community, mainly in Europe, the US and Japan, rather than in other developing countries. Dependence on imported equipment from these countries, and their dominance in scientific publishing, increased the importance of close relationships with their scientists. Even while some South African researchers did world-class research and participated in international scientific organisations, the general relationship between South African researchers and their Western counterparts was generally not an equal one. The relationship between local and international research institutions has been described as a form of ‘scientific imperialism’.

in which funding was usually controlled by wealthy Western institutions, and the research agenda was set by them; in the worst cases, research findings from external or collaborative programmes were therefore not relevant or implementable in addressing local problems, and local research capacity was not developed (Tucker and Makgoba, 2008).

The burden of disease in South Africa is linked to its history of racial and gender inequality, oppression and enforced labour migration, as well as to some of the failures of post-apartheid independence. It is characterised by high levels of both communicable and non-communicable diseases, particularly those which are related to poor working conditions and domestic poverty, gender-based violence and injury. There have historically been significant racial and gender differences in disease burden and life expectancy, and these remain today (Coovadia, 2009).

Medical research in South Africa did not address the national burdens of disease equitably for most of the 20th century. Researchers and their funders were often interested in the problems of the African majority primarily to support white-owned industry. South Africa's colonial and apartheid economy was aimed at minerals and resource extraction, while industrial development was aimed at import substitution as early as the 1920s and did not shift to export-oriented industrialisation until the early 1990s. Mining was dependent on cheap black labour, and import substitution was highly dependent on skilled (white) labour and capital-intensive production processes (Altman and Mayer, 2003, cited in Kraak, 2004). Much of the health services infrastructure was thus located in urban areas serving the needs of the white population – the basic health needs of rural Africans were not prioritised. Mines were willing to address migrant workers' health needs in the short term through the provision of vaccines and by sending sick workers home, but avoided paying for more expensive long-term health benefits which required the provision of better working conditions and sick benefits.

Because of its increasing status as a symbol of modernity, medical science also played a broader political role on the international stage, representing South Africa as a mature nation worthy of independence and respect

within the British Empire. Public institutions like museums, universities, hospitals or mental asylums helped the small South African colonies in the late 19th century to represent themselves as civilised, mature outposts of the Empire which deserved a degree of independence in local governance. During his period of office as prime minister, J.C. Smuts, himself a noted philosopher and amateur scientist, used national scientific achievements to position South Africa as a nation deserving of respect within the British Commonwealth, capable of bringing Western 'civilisation' to the country through industrial development and judicious handling of 'the native question' (Dubow, 2006). In South Africa, medical research was thus seen as playing a particular role in potentially returning "to the rest of the world some of the benefits which she has received from the development of scientific research in overseas countries" (Schonland, 2005). Scientific research that was valued and validated in the developed world was equally important to the apartheid government in its quest to display South Africa's modernity to the world and encourage its acceptability (Logan, 2003). In 1967, L. Munnik, MEC for Hospital Services, informed the prime minister, B. J. Vorster, that Barnard had put South Africa and its medical institutions "on the world map" (Logan, 2003). Funding was not therefore denied to broad-based clinical research, though the government and its agencies were partisan or narrowly focused on their electorate in some research-funding decisions (Dubow, 2006). Since the end of apartheid, the nature and quality of scientific research have continued to be important in the debate about South Africa's 'new' national identity, and its intellectual and political standing in the world. In 1996, T. Mbeki, then deputy president, envisaged a key role for science and technology in aiding the intellectual and spiritual renewal of Africa – the **African Renaissance**.

The scientific revolution thus marked an important turning point in the way doctors have understood disease and its treatment in Europe, and coincided with the development of a South African medical profession which had strong connections to European science. Historical investment in medical research in South Africa developed a strong scientific base that can be used to promote clinical research, and national health, in the future. The fact that the history of medical science is as much a political as a scientific history renders it necessary to re-think many of the trajectories of the past.

THE LEGACY OF RACISM AND INEQUALITY IN MEDICAL RESEARCH

The first Western-trained doctors working in South Africa were ships' surgeons employed by the Dutch East India Company (DEIC), whose willing or unwilling clients would have included Company employees and slaves. A few of the early settlers were also doctors, with private practices among burghers and DEIC officials. The number of private practitioners expanded in the 19th century, and many of them also worked as district surgeons and in new state-funded hospitals. As missionaries or state employees, or even as private practitioners with roles in magistrate's courts, Western-trained doctors were often linked to other political and cultural interventions of the colonial order. Many of these **public health interventions** were biased against working-class people, and linked to the political agenda of the state, for example the racial segregation within towns. There was a degree of popular resistance to some colonial public health interventions, such as the treatment of sex workers in Lock Hospitals in the mid-19th century (Van Heyningen, 1984), the compulsory segregation of people with leprosy, especially between 1891 and the 1910s (Deacon, 1994), and urban removals of black people associated with plague outbreaks in the early 20th century (Swanson, 1977), but these did not significantly disturb the system as a whole.

Strong state support for the Western **medical profession** dates back to 1807 in the Cape Colony, when European-trained doctors secured state support for a monopoly on legal practice. This allowed the profession to entrench its position within both private practice and public institutions, even while most inhabitants still used traditional medicines. Similar legislation was passed in England only half a century later, in 1858, but even then British legislation did not ban unlicensed medical practice, as Cape law had done. Under Cape law, nurses and midwives were registered from 1891, some years before their British counterparts received legal protection and government ratification of their training (Deacon, 2004). From the 18th century, Western-trained doctors attended black and white patients, especially in dealing with diseases associated with colonialism (smallpox, measles, and tuberculosis) and those

requiring surgery (Digby, 2006). They distanced themselves from indigenous healers, who were banned in some parts of the country. Yet Western medicine has never universally displaced other forms of health care in South Africa, and the public to this day continues to seek assistance from alternative and traditional healers (Peltzer, 2008). The relationship between alternative and orthodox medical practitioners remains adversarial, even as the post-apartheid state set out to regulate rather than prohibit non-evidence-based medical practice, both in its alternative Western forms and indigenous African practices (Wreford, 2006).

By the early 20th century, **public health policies** were linked to racial segregation and this affected public perceptions of the biomedical system. For example, the Transvaal Native Pass Act of 1909 linked permission for Africans to work in urban areas with compulsory smallpox vaccination and inspection for tuberculosis (TB) and syphilis. Tax collection by magistrates was also linked to examinations to detect sexually transmitted infection (STI) and smallpox vaccinations. Africans with syphilis were either isolated on their homesteads or brought to the local jail for treatment (Jochelson, 1999). The Public Health Act of 1919 amended some overtly racist provisions, but blacks were still treated very differently from whites: the process of identifying and treating STIs among Africans, for example, was 'coercive and authoritarian' and focused on fitness to work (Jochelson, 1999). The new welfarism in public health policy towards Africans that emerged in the 1940s was focused mainly on urban Africans (Jochelson, 1999), and provision for birth control, for example, was linked to political agendas such as the restriction of African population growth under apartheid.

In the 19th and early 20th century, South African medical research was also frequently explicitly racist (Dubow, 1995). After the 1940s, although research was not free of racism, clinical researchers began to position themselves within a growing international body of universal scientific research in which racial differences were thought to exist but were not explained by immutable and hereditary racial typologies (Stepan, 1982). In this, the researchers concerned were (ironically) supported by a racist government that valued South Africa's

international scientific reputation and generally refrained from using medical science as a justification for apartheid or white supremacy. Yet even as explicit racism became unacceptable in scientific publications, racial discrimination continued at a social level (alongside gender and class), and influenced the question of who would be likely to be trained or employed to do research, in what professional capacities, and the way in which research data were investigated (Deacon, 2008).

The **demographics** of the medical profession (and by extension, medical researchers) in South Africa, viz. predominantly middle-class white men, affected the approach (including the languages) used in medical research and how it was perceived by the general public. Until the first medical school was opened in Cape Town in the early 20th century, Western-trained doctors came to South Africa from Europe and South African-born doctors trained in Europe. Although black students and later women were accepted in European medical schools, it was expensive for locals to go and study abroad, so most of those who did so were from white families with the means to do so. Only a handful of black and white women doctors were formally registered for practice in South Africa by 1900. Science formed an important pillar of middle-class white identity in South Africa from the 1920s, and even today, white citizenship in South Africa continues to be framed in terms of skills and expertise (Dubow, 1995; 2006). In the course of the 20th century, barriers to the entry of black people into the medical profession increased further until this was reversed gradually in the 1980s. Barriers to the entry of white women began decreasing much earlier. Even when black matriculants were able to cross educational and class barriers in entering medical schools, they were limited to a few schools across the country and excluded from white residences on campuses (which made their education more expensive). They were not allowed to participate in the full range of educational activities (being excluded from white wards and autopsies on white patients) and were excluded from some of the informal networks of support and patronage from white doctors (although some white doctors made special efforts to tutor black students). After graduation, professional specialisation was difficult because black-owned offices could not be opened in white areas, black doctors could

not attend white patients, and specialist hospital appointments for black doctors were limited (Deacon, 2008). Today, the majority of medical students and specialists in training at South Africa medical schools are not white, and the opportunity to tap the entire talent of the population for health care and its necessary 'yeast' (clinical research) finally exists. Making this happen, however, requires thorough situational investigation and analysis, which the present report sets out to provide.

As an example of the non-trivial nature of the challenge, there are the facts that past **institutional investments** in research were unequally allocated, and that this inequality continues to mark medical research outputs today. As Volmink (2005) has noted, "Research capacity — comprising the institutional and regulatory frameworks, infrastructure, investment, and sufficiently skilled people to conduct and publish research — varies widely across African countries." Even within a country like South Africa, which performs reasonably well overall in terms of national investments and productivity in science and technology, long-standing inequalities between different universities affect current research outputs. Under apartheid, "Institutional differentiation was achieved through a binary divide between universities and technikons (polytechnics) and also, unacceptably, by building institutions for different race groups – those for whites were well-resourced urban, often research-oriented institutions, and those for other races were poorly supported, mostly teaching institutions, often in rural areas" (Cloete, 2008).

The democratic transition of 1994 brought a new focus on **primary health care** and equity in the sector, which, along with the much more widespread provision of social grants, was designed to reduce disease and poverty and redress socio-economic imbalances. Many positive benefits have resulted. More clinics have been built, and important health care services such as immunisations and key drugs have become more accessible and available to the poor. Professional organisations and policies have been reoriented, new categories of health care worker have been created and compulsory community service has been instituted for doctors and nurses, among others. Yet the benefits of redistributive policies have been limited by "inadequate

human resource capacity and planning, and poor stewardship, leadership and management," exacerbated by problems such as increasing levels of medical emigration. The resource gap between the public and private health care systems has increased, and there is at present a staffing crisis in the public health service, especially at district and community-level facilities (Coovadia, 2009). The inequalities in the South African health care system, and to some extent in its research capacity, have thus not been reversed, and in some cases they have increased or have been entrenched.

TWENTIETH-CENTURY SOUTH AFRICAN MEDICAL RESEARCH: ACHIEVEMENTS AND LIMITATIONS

Although South African scientific research was relatively low-key during the 18th and 19th centuries, **clinical research in South Africa** came into its own in the second half of the 20th century. South Africa was considered a good natural laboratory for acquiring knowledge about certain diseases that were relatively rare in Europe. Research units and centres were established, and local funding became easier to acquire. Government and the mining houses funded most medical research and health care provision. Government investment in medical research began with the establishment of the Colonial Bacteriological Institute in 1891 for laboratory work on rinderpest and leprosy (Spinage, 2003). The **South African Institute for Medical Research (SAIMR)**, established in 1912, was funded partly by the Chamber of Mines (Meiring-Naudé and Brown, 1977). By mid-century, the **Council for Scientific and Industrial Research (CSIR)** provided a more general channel for government funding of medical research, leading to the hiving-off of the **Medical Research Council (MRC)** from the CSIR in 1969, and its establishment in Cape Town.

The mining industry and government encouraged and influenced research on asbestosis, pneumococcal pneumonia, tuberculosis and silicosis, all of which affected mineworkers (McCulloch, 2005; Katz, 1995; Packard, 1989). A 'TB Commission' was created by the Union Government in 1912, and a 'TB Research Committee' was established by the Union Government and the Chamber of Mines in 1926, collecting considerable data about the

epidemiology and pathology of tuberculosis. Local scientists, funded by the mining companies, developed a physiological theory of black susceptibility to the disease, but there was little consensus about how to manage the problem until the use of specific antibiotics in the 1950s (Packard, 1987). By this time, racial explanations of disease were becoming scientifically unacceptable and environmental theories of the cause of TB on the mines were reasserted. A TB Research Unit was established at the CSIR in 1963.

THE DEVELOPMENT OF A PNEUMOCOCCAL PNEUMONIA VACCINE

In the early 20th century, A. Wright, from St Mary's Hospital Medical School in London, was asked to lead a South African project to develop a pneumococcal pneumonia vaccine, based on his experience with typhoid fever vaccines. The vaccine trial, published in 1914, involved about 50 000 gold miners, and showed a decrease in pneumonia among those receiving the vaccine. In 1917, S. Lister, one of Wright's researchers based at the SAIMR, "identified the multiple serotypes causing infection in miners ... and included them in a single inactivated whole-cell vaccine", again tested on mineworkers (Kazanjian, 2004). The success of this vaccine was disputed in various quarters. Packard (1993) suggests that it was the mining companies' reluctance to invest in better working conditions for migrant labourers that encouraged their initial investment in pneumonia vaccines – doing so medicalised the problem and limited their liability to improve living conditions and wages. He suggests that mining funding for the SAIMR vaccine initiative also fuelled their optimism about the vaccine. The widespread use of sulphonamide therapy after 1939 and antibiotics in the 1940s later overshadowed the use of vaccines to treat pneumonia (Packard, 1993). South Africa was the site of a major pneumococcal vaccine trial led by R. Austrian, a US doctor, in the 1970s. On the basis of this trial, the US Federal Drug Administration (FDA) licensed a fourteen-valent polysaccharide vaccine to Merck in 1977 (Kazanjian, 2004).

Unfortunately not all the research that was done on these diseases resulted in better working conditions, or in reduced prevalence rates in the general population (Butchart, 1996). Packard (1989) argues that TB prevalence among Africans may not have declined as significantly after the 1950s as the MRC's TB Research Institute suggested, because the quality of the prevalence data collected was poor and not comparable over time. Although there was considerable investment in TB research in South Africa, there was little progress in reducing the burden of disease from TB because of the socio-economic conditions under which most Africans continued to live. Similarly, although South African researchers were central players in the global circulation of scientific knowledge about asbestosis and silicosis, this information was often silenced at home. Researchers such as the mine medical officer G. Slade showed in 1931 that there was a high incidence of asbestosis in black mill workers, for example, but he concluded because they did not complain that the disease was clinically more benign than in the UK. Scientific data on asbestosis prevalence was suppressed by industry in the 1960s, researchers at the Pneumoconiosis Research Unit (PRU) in Johannesburg did not include black workers in their longitudinal studies of asbestosis, and surveillance data kept by the mining companies were inaccurate. Because these companies had little interest in improving working conditions, and the affected black workers were denied political power, research did not lead to improved measurement or management of the problem (Braun, 2008; Myers, 2006).

Some of the earliest health research areas funded by the CSIR focused on **parasitic diseases** such as amoebiasis and bilharzia, for which research units were established in 1949. Under Elsdon-Dew, South African research made a major international contribution to the diagnosis and treatment of amoebiasis in the 1950s and 1960s (Schutte *et al.*, 1988). In the SAIMR in the 1930s, Elsdon-Dew had already been internationally recognised for his pioneering work on blood typing (Gear, 1988). A. Theiler, who established the Onderstepoort veterinary research institute, laid the foundation for work on **viral diseases** in South Africa among others. His son, M. Theiler, received the Nobel Prize for his work in the US in developing an effective yellow fever vaccine. The SAIMR developed typhus and influenza vaccines for allied troops in World

War II, and later yellow fever and polio vaccines (Dowdle, 1988). M. Isaacson later worked on a plague vaccine there in the 1970s (Hallett *et al.*, 1973). The Poliomyelitis Research Foundation (PRF) laboratories were opened in 1953, where J. Gear led research culminating in the production of a polio vaccine at the same time it was developed in the US (Metz, 1988). This laboratory became the National Institute for Virology (NIV) in 1976, and the National Institute for Communicable Diseases (NICD) from 2002, working more generally on prevalent infectious diseases (Schoub, 2003). An MRC **HIV/AIDS research programme** was initiated in 1987, and many groups spread across the country now do world-class research in this area. The South African AIDS Vaccine Initiative (SAAVI) was formed in 1999 as a lead programme of the MRC of South Africa. It coordinates the research, development and testing of AIDS vaccines in South Africa (<http://www.saavi.org.za/index.htm>).

Research on **nutrition** was partly sparked by the needs of the mining companies, and to address concerns from the early 20th century onwards that both white and black South Africans were deteriorating physically (Wylie, 2001). Nutrition was also a major research focus in the UK in the first half of the 20th century, prompted by the poor quality of military recruits. Scurvy was a major problem on the Witwatersrand mines from the very beginning, as the mineworkers' diet mainly consisted of maize meal. Researchers like F. Fox (Brock, 1979) and M. Delf studied scurvy at the SAIMR in the 1920s, conducting fieldwork in the Eastern Cape, analysing samples in the Pretoria laboratories and making recommendations for feeding miners on the Rand (Malan, 1988). Fox argued that the problem did not lie in racial predisposition to scurvy, or predisposing conditions in rural areas, as others had argued before and were to argue again, but in the low vitamin C content of mine rations and poor working conditions (Malan, 1988). A series of major nutritional studies were initiated in 1937, involving S. Kark and J. F. Brock, who were early public health activists in the country. Brock established the connection between **protein malnutrition and kwashiorkor**; the research of his group on malnutrition, particularly kwashiorkor and scurvy, was funded by the Union Department of Health, the CSIR and the WHO (Louw, 1969), and developed an important later focus on paediatric malnutrition. The CSIR established a National Nutrition Research

Institute in the 1950s, which came under the MRC in 1969. Researchers in the Institute demonstrated links between dietary fat, lipid metabolism and **coronary heart disease** (Brock, 1979). In the 1960s, work on **iron overload** in Africans caused by iron release from food containers and cooking utensils showed that a 'Westernised' diet raised the risk of bowel cancer (Malan 1988). Research that identified the specific geographical locations of mineworkers suffering from **liver cancer** (Inhambane Province of Mozambique) in the 1960s pointed the way to the finding that dietary aflatoxins were linked to liver cancer, and to further internationally recognised research on food-borne **fungal toxins** in South Africa (Marasas, 1988).

Nutritional and **epidemiological research** in South Africa established a clear connection between living conditions and disease, and made the case for preventive health care by the end of the 1950s, but this approach lacked state support and was hampered during the conservative 1960s. Key epidemiological research included the comprehensive Gluckman Commission of 1942-44 and fieldwork conducted in the 1950s by Burrell, Oettlé and Higginson (Bradshaw and Yach, 1988). The epidemiological work in South Africa during this period in fact helped to establish the discipline internationally. The early public health initiatives of the 1940s faded under apartheid (Marks, 1997). Work done at the SAIMR and Medunsa produced some research that "missed the wider social context of national health" (Wylie, 2001). A. Walker's research, for example, focused on the limitations of public health interventions and the importance of educating the poor, suggesting that malnutrition in poor African children should not be measured against Western standards (Wylie, 2001). The Department of Health de-listed kwashiorkor as a notifiable disease in 1968 and the MRC shifted funding away from diseases of poverty like kwashiorkor, towards the study of diseases of affluence (e.g. the effects of high cholesterol) in the 1970s (Wylie, 2001; Baldwin-Ragaven *et al.*, 1999). There were, however, broader trends towards public health and epidemiological research in the 1970s and 1980s that affected research in South Africa and were linked to anti-apartheid discourse. Building on trends in the WHO towards public health, a strong critique developed of hospital-based medicine in South Africa (Niewijk, 1999). After 1994, more attention was paid to **public health research** as the

health system was reoriented towards the needs of the general population. The MRC and other institutions restructured their research to take account of national health priorities.

In general, disease-specific investigations were favoured over public health research during the colonial and apartheid years, a pattern that continues to some extent today. In the 1950s and 1960s, an era of heroic surgery internationally (Amsterdamska and Hiddinga, 2000), heart, liver and kidney **transplants** were an important focus of South African clinical research. The world's first open-heart transplant in 1967, led by C. N. Barnard, was built on decades of work on vascular and cardiac disease by R. Goetz and V. Schrire. It was followed by other transplant firsts at Groote Schuur Hospital, where B. Cohen performed the world's first vascularised human fallopian tube transplant in 1975 (Groote Schuur Hospital Annual Report, 1975). These breakthroughs depended not only on clinical research, but also on international collaborations and on technical advances such as the development of the heart-lung machine in the US. In conducting transplants, the less litigious environment around medical practice in South Africa made it easier for surgeons to risk a 'first' (Logan, 2003). Following the heart transplant in 1967, it was relatively easy for local institutions to find funding to support cardiology research. The mining industry, for instance, came forward to fund a Research Centre for Cardiac Disease and Organ Transplantation (Cape Argus newspaper, 1970). From the 1960s, South African immunology research was closely linked to the needs of the transplantation programme. M. C. Botha and E. du Toit became well known for their study of rare MHC (Major Histocompatibility Complex) antigens in the San and other South African populations. A. Myburgh and J. Smit at the University of the Witwatersrand (Wits) experimented with total lymphoid radiation as a technique for the control of organ rejection (Dowdle, 1988).

Disease-specific investigations were conducted into **genetic diseases** and diseases of lifestyle including porphyria, cancer and cardiac and liver disease. Genetic abnormalities in small populations who then intermarry over decades can create a situation (a founder effect) in which certain genetic diseases

become unusually prevalent (Botha and Beighton, 1983). Afrikaners (and a small group of Africans in the Eastern Cape) show unusually high levels of the disease **porphyria** (Day, 1988). Recognition of the problem in the Afrikaner population attracted government attention and research funding in the 1950s, at a time when it was also receiving some international attention. In 1957, the CSIR funded a Porphyria Research Group at the University of Cape Town (UCT) under L. Eales, which pioneered internationally and locally useful new techniques in porphyria diagnosis and classification in the 1960s and 1970s (Day, 1988). Following on from earlier physical anthropology studies, genetic research on these and other more common diseases formed a cornerstone of South African research activity from the 1960s onwards, marked for example by the work of P. Beighton on **skeletal diseases** in Cape Town, and the work by T. Jenkins and H. Soodyall on **human population genetics** at the SAIMR and Wits University. Familial **lipid disorders** associated with early heart attacks were studied in detail by W. Gevers and A. E. Retief. Cardiac and liver diseases have continued to be a research focus at academic hospitals such as Groote Schuur (Bonner *et al.*, 2007). Today, research on coronary heart disease, cancer, diabetes and obesity has become more relevant to the current burden of disease as they have become more common in black communities (Steyn *et al.*, 2006). Many poor black communities also experience a high incidence of **rheumatic fever** which causes heart disease (Commerford, 1988).

South African researchers contributed to the development of some major innovations in **diagnostic medical equipment**, perhaps because this was particularly expensive to import, and in diagnostic techniques, because of a strong link between preclinical and clinical research. Besides the examples mentioned above, H. Zwarenstein and H. Shapiro pioneered a method for the diagnosis of human pregnancy using frogs in 1933 (Louw, 1969). R. Goetz, based at UCT from 1937 until the late 1950s, earned an international reputation for his work on digital plethysmography (the measurement of changes in blood flow in the fingers or toes), the sympathetic control of peripheral blood vessels, Raynaud's disease, diabetic gangrene and progressive systemic sclerosis (Louw, 1969). His plethysmograph (1943) assisted in the diagnosis of peripheral vascular disease (Goetz, 1948). Later work at the MRC in Johannesburg on

blood circulation led to further pioneering work on the use of radioactive microspheres for the measurement of tissue blood flow (Rosendorff, 1988). The 1979 **Nobel Prize for Medicine or Physiology** was a joint award for **computerised axial tomography (CAT)** scanning, shared by a South African, **A. Cormack**, who had become interested in the mathematical problem of creating a correct radiographic cross-section in a biological system when he worked as a hospital physicist at Groote Schuur Hospital in the mid-1950s. A British computer specialist later used Cormack's ideas to develop the first CAT scanner machine (Cormack, 1979; Vaughan, 2008). A recent collaboration between the Groote Schuur Hospital Trauma and Radiology departments and the De Beers Diamond Mining Organisation resulted in the development of Lodox, a special low-dose radiation X-ray screening apparatus that can accurately pinpoint foreign objects such as bullets in trauma patients and monitor organ function for research purposes (Groote Schuur Hospital Annual Report, 1999/2000).

In spite of the idea that medical research was important for South Africa's international reputation and that promoting science would help transformation, state expenditure on medical research in academic hospitals decreased from the beginning of the 1980s. This trend towards disinvesting in medical research was exacerbated by the redistribution of state investment in the health care system towards primary health care after 1994 and the simultaneous stagnation of public health care spending (Coovadia, 2009). An increasing burden of health care service provision falling on health care workers in the public service, has left little in the way of time and resources for research.

RANDOMISED CONTROLLED CLINICAL TRIALS

The first **randomised controlled clinical trial** in the modern era was published in the UK on the use of streptomycin in the treatment of TB. The design of the trial followed the work of R. A. Fisher in agriculture which emphasised the importance of randomisation, and it became a model for future randomised controlled trials (Booth, 1993). Clinical trials became ever more widely used in the latter part of the 20th century, with evidence-based medicine driving public health provision and the expansion of the pharmaceutical industry.

In spite of increased funding and emphasis on clinical trials, however, many of the therapies used in biomedical practice, well into the present day, have not been subject to formal clinical trials. Trial results are also not always implemented.

More clinical trials began to be conducted in developing countries such as South Africa after rules on the use of foreign data in pharmaceutical research were liberalised in places such as the US (Ford and Tomossy, 2004). Fewer randomised clinical trials are being published in leading medical journals such as the *South African Medical Journal* (Pienaar *et al.*, 2002), but this may be because trial results are not being published, or they are being published elsewhere.

A further two studies have attempted to document the number and type of trials conducted within South Africa. Eight hundred and fifty-eight randomised controlled trials were published in the *South African Medical Journal* since 1948, mostly in the period 1968–1987: only two such trials were identified before 1957 (Pienaar *et al.*, 2002). In a subsequent and fuller analysis of 1 179 randomised controlled trials done on sub-Saharan African people from 1965–1999, it was found that only 12 trials were published between 1949 and 1964 – about half were conducted in South Africa, and the number of trials increased over time as shown in Figure 2.1 (Isaakidis *et al.*, 2002).

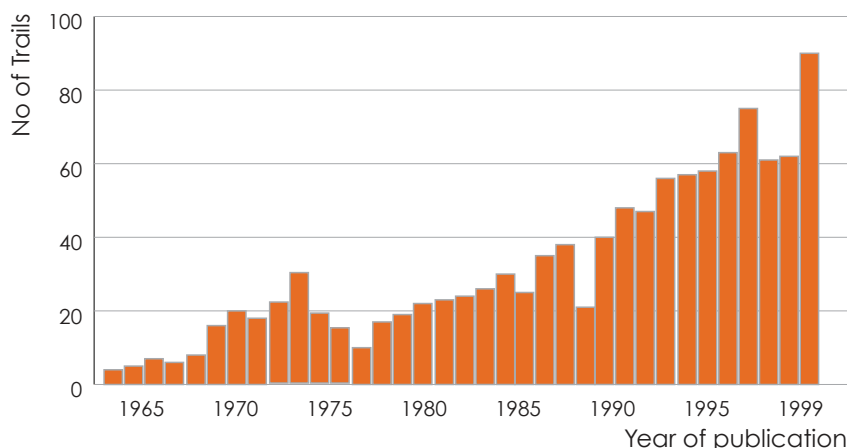


Figure 2.1: Number of randomised controlled trials in sub-Saharan Africa from 1965–1999 (Isaakidis *et al.*, 2002: 324)

Currently no comprehensive database of completed trials exists. The National Department of Health has established a publicly accessible **National Health Research Database** (NHRD) (<http://www.researchdatabase.org.za>) but it is not possible to search this specifically for clinical trials. The primary purpose of the NHRD is to provide a central storage database of all health research conducted in South and southern Africa. Closely allied to this is the NHRD's function as a knowledge management tool for health research that is planned, produced, published or documented by both South African and other researchers conducting research in southern African communities and facilities. Possible addition of study type and/or study design to the search engine of this database would greatly assist in the retrospective documentation of clinical trials.

Historically, clinical trials in South Africa have tended to be hospital based, focused on testing treatments rather than on prevention measures, and on chronic rather than infectious diseases (Pienaar *et al.*, 2002). The spread of trials conducted does not accord with the burden of disease in the country

(Isaakidis *et al.*, 2002). Problems in addressing burden of disease may arise not only from gaps in medical knowledge about how to manage the disease, but also from problems of implementation including political will. This has been well demonstrated in state attitudes towards the use of anti-retrovirals in the treatment of HIV/AIDS since the 1990s (Nattrass, 2006; Hirschhorn *et al.*, 2007).

The long history of state support for evidence-based medicine, the historically mainly white and male composition of the pool of medical doctors, and the often adversarial relationship between medicine and indigenous healing traditions, have influenced experiences and perceptions of medical research and willingness to participate in clinical trials (Baldwin-Ragaven *et al.*, 1999). Doctors and other health care workers were complicit in the mistreatment of detainees in the 1980s, and research was explicitly used to further the aims of the apartheid government through a secret chemical and biological warfare programme, Project Coast, whose extent only became widely known with the trial of Wouter Basson (Gould *et al.*, 2002). Given this history, the Truth and Reconciliation Commission recommended a focus on primary health care, increasing the number of black students and health care professionals, training in human rights and ethical research practices, and the prevention of human rights abuses (Baldwin-Ragaven *et al.*, 1999). Continued vigilance has to be exercised in the light of recent fraudulent clinical trials by W. Bezwoda (Horton, 2000) and state support for Virodene and the multivitamin preparations in treating AIDS in spite of opposition from the Medicines Control Council and the scientific community (Youde, 2007). There have also been concerns about deaths arising from poor safety and informed consent procedures in some of the HIV/AIDS trials (Sidley, 2000).

CONCLUSIONS

South African medical science was strongly influenced by its colonial context and by the needs of local industry and general economic development. This broader political and economic context affected what research was done, how it was done, how it was used and who did the research, contributing to a history of unequal access to health care and inappropriate priority setting in

medical research. Understanding this context does not lessen the value of the research that was done, but helps us to understand the nature of some current problems, including the unusually diverse and heavy burden of disease, the mismatch between local burden of disease and medical research, a racially and gender-skewed cohort of medical researchers, under-developed institutional capacity in the production of research and, in some cases, public mistrust of medical research.

The mining industry and government encouraged and influenced medical research (especially of vaccines as potential 'magic bullets') in South Africa. Because of social disruption caused by migrancy, land dispossession and poor working conditions, there was a high prevalence of pneumonia, tuberculosis and silicosis in mineworkers, and nutritional, parasitic and viral disease in mineworkers and farm workers. Internationally, research on these health problems generated highly regarded scientific data, partly because of the large sample sizes, but it did not always lead to lower disease prevalence in the general population. Nutritional and epidemiological research in South Africa during the 1940s and 1950s was also internationally recognised, but in spite of early initiatives such as the Gluckman Commission, a preventive approach to health care did not emerge until the 1990s.

South African medical research focused more on hospital-based medicine and diseases of affluence than was warranted by the burden of disease at the time, although some of this research has become more relevant today. Diseases affecting more white than black South Africans in the past, such as porphyria, coronary heart disease, diabetes and myocardial infarction (heart attacks), received significant, although not exclusive, research attention under apartheid. Equipment and funding shortages contributed to innovation in locally developed diagnostic equipment. Local genetic diversity and founder effects in the Afrikaner population, reflective of the increased influence by Afrikaner researchers and institutions under apartheid, fostered important South African research strengths in blood typing, medical genetics and certain genetic diseases. Considerable funding was available for transplant-related research after the first heart transplant in 1967, and this encouraged world-class research in heart and liver disease, and also in immunology and genetics.

Public perceptions of clinical research today are still negatively affected by the close historical relationship between medicine and the colonial state, the often adversarial relationship between medicine and indigenous healing traditions, racism and unethical practice in medical research (real and perceived), and the skewed demographics of medical researchers. Yet there is hope. From the beginning of the 20th century, medical researchers in South Africa began to develop a strong scientific base that can be used to build clinical research in the future. This scientific infrastructure has been gradually reorienting itself to the current burden of disease within a more democratic political context that prioritises the health needs of the majority, promotes more community involvement, and addresses the skewed demographics of health researchers. The challenge now is to find ways of promoting clinical research that builds on the advantages of past investment while actively addressing the legacy of colonialism and racism.

FINDINGS

1. Medical researchers in South Africa from the beginning of the 20th century began to develop a strong scientific base for clinical research in terms of personnel and infrastructure, conducting important investigations into a wide range of medical problems.
2. The burden of disease in South Africa is significantly linked to its history of racial and gender inequality, violence, oppression and enforced labour migration, and to some of the failures of post-apartheid independence. It is characterised by high levels of both communicable and non-communicable diseases, particularly those that are related to poor working conditions and poverty, gender-based violence and injury.
3. Because of the colonial context, clinical investigations (with some notable exceptions) were largely driven by the needs of the mining and agricultural industry, or focused on curative medicine in urban areas. Thus, clinical research did not always improve the health of the population as whole.

4. Clinical research in the apartheid years was conducted by a cohort of investigators who were mainly white and male within a system that provided racially unequal access to health care and research training. Institutional capacity to conduct clinical research was concentrated in a few historically white institutions.
5. Some clinical research in the colonial and apartheid era was racist and unethical, facilitated by an environment of racial inequality, discrimination and high status and wealth differentials under an oppressive state.
6. After 1994, significant strides have been made in reorienting health care and medical research towards the needs of the majority at a policy level, but in practice the tangible benefits of this have been limited by reduced government support for medical research within the health care system, a weak education system, and poor management of existing resources within the health care system, in the face of new challenges such as HIV/AIDS.

RECOMMENDATIONS

1. Clinical research should be repositioned within a more democratic political context to build on the advantages of past investment while actively addressing the legacy of colonialism.
2. Clinical research should actively contribute to the improvement of the health of the nation by actively addressing the largest burdens of disease.
3. The training and promotion of clinical researchers should actively seek to address racial and gender imbalances, and ensure that strong intellectual leadership is built.
4. The funding of clinical research should actively seek to develop strengths wherever these can be best and most sustainably built.
5. Clinical research should be based on strong ethical codes of conduct.

REFERENCES FOR CHAPTER 2

- Altman, M. and Mayer, M. 2003. In: A. Kraak (Ed.), *An Overview of South African Human Resources Development*, HSRC Press. p. 52.
- Amsterdamska, O. and Hiddinga, A. 2000. *The analysed body*. In: J. Pickstone and R. Cooter (Eds), *Medicine in the Twentieth Century*. London: Harwood.
- Baldwin-Ragaven, L., De Gruchy, J. and London, L. 1999. *An Ambulance of the Wrong Colour: Health Professionals, Human Rights and Ethics in South Africa*. Cape Town: UCT Press. p. 26.
- Bonner, P., Esterhuysen, A. and Jenkins, T. 2007. *A Search for Origins*. Johannesburg: Witwatersrand University Press.
- Booth, C. C. 1993. Clinical research. In: W. F. Bynum and R. Porter (Eds.), *Companion Encyclopaedia of the History of Medicine*. London: Routledge. Vol. 1, pp. 205-229.
- Botha, M. C. and Beighton, P. 1983. Inherited disorders in the Afrikaner population of Southern Africa: Part I. Historical and demographic background, cardiovascular, neurological, metabolic and intestinal conditions. *South African Medical Journal*. 64(16): 609-612.
- Bradshaw, D. and Yach, D. 1988. Epidemiology: Disease patterns point the way to priorities. In: A. J. Brink (Ed.), *South African Medical Research: Twenty Years of Growth*, Pinetown: Owen Burgess. pp 85-91.
- Braun, L. 2008. Structuring silence: Asbestos and biomedical research in Britain and South Africa. *Race and Class*. 50: 59-78.
- Brock, J. F. 1977. Some highlights of Medical Research in South Africa. In: Brown, A. C. (Ed.), *A History of Scientific Endeavour in South Africa*. Cape Town, Royal Society of South Africa: Rustica Press. pp. 192-213.
- Burrows, E. 1958. *A history of medicine in South Africa*. Cape Town, Amsterdam: Balkema. pp. 65, 98-99, 170.
- Butchart, A. 1996. *The Industrial Panopticon: Mining and the medical construction of migrant African labour in South Africa, 1900–1950*. *Social Science & Medicine*. 42(2): 185-197.
- Cape Argus newspaper, 12 May 1970.
- Cloete, N. 2008. Institutional diversity, programme differentiation. *University World News, Africa edition*, January. p. 7.
- Cluver, M. A. and Smith, A. 1988. 1797– 1872. In: A. J. Brink (Ed.), *South African Medical Research: Twenty Years of Growth*, Pinetown: Owen Burgess. pp. 147-148.
- Commerford, P. J. 1988. Cardiology: recent advances and their implications. Inaugural lecture as UCT Helen and Morris Mauerberger Professor of Cardiology, 23 March.
- Cook, H. 2007. *Matters of Exchange: Commerce, Medicine and Science in the Dutch Golden Age*. Yale: Yale University Press.
- Coovadia, H. 2009. Hoosen Coovadia: An icon of South African health. *Lancet*. 374(9692): 777.

- Cormack, A. M. 1979. Nobel Foundation website, autobiographical note. Available at: http://www.nobelprize.org/nobel_prizes/medicine/laureates/1979/cormack-autobio.html
- Day, R. 1988. Porphyria: the South African perspective. In: A. J. Brink (Ed.), *South African Medical Research: Twenty Years of Growth*, Pinetown: Owen Burgess. pp. 149-156.
- Deacon, H. J. 1994. A history of the medical institutions on Robben Island, 1846-1910. PhD thesis, University of Cambridge.
- Deacon, H. J. 2004. Introduction: the Cape Doctor in the nineteenth century'. In: H.J. Deacon, E. van Heyningen and H. Phillips (Eds.) *The Cape Doctor in the Nineteenth Century: A Social History*,. Amsterdam: Rodopi. pp. 17-43.
- Deacon, H. J. 2008. The fighting arm of the medical profession: Clinical research at Groote Schuur Hospital. In: H. Phillips and A. Digby et al. (Eds.), *In the Heart of Healing: Groote Schuur Hospital, 1938-200*,. Johannesburg: Jacana.
- Digby, A. 2006. *Diversity and Division in Medicine: Health Care in South Africa from the 1800s*. Oxford: Peter Lang. p. 62.
- Dowdle, E. 1988. Immunology in South Africa. In A. J. Brink (Ed.) *South African Medical Research: Twenty Years of Growth*. Pinetown: Owen Burgess. pp 221-228.
- Dubow, S. 1995. *Scientific Racism in Modern South Africa*. Cambridge: Cambridge University Press.
- Dubow, S. 2006. *Science, Sensibility and White South Africa, 1820-2000*. Chapter 5: *A commonwealth of knowledge*. Oxford: Oxford University Press. pp 253-254.
- Ford, J. and Tomossy, G. 2004. Clinical trials in developing countries: The plaintiff's challenge. *Law, Social Justice and Global Development Journal*. 7(1).
- Gear, J. H. S. 1988. Ronald Elsdon-Dew (1909-1984). In: A. J. Brink (Ed.) *South African Medical Research: Twenty Years of Growth*, Pinewood: Owen Burgess. pp. 19-20.
- Goetz, R. H. 1948. Clinical plethysmography. *South African Medical Journal*. 22(13): 422.
- Gould, C., Folb, P. and Berold, R. 2002. *Project Coast: Apartheid's chemical and biological warfare programme*. United Nations Institute for Disarmament Research.
- Groote Schuur Hospital Annual Report, 1975.
- Groote Schuur Hospital Group Annual Report, 1999/2000. p. 8.
- Haagsche Genootschap tot Verdediging van de Christelijke Godsdienst, Commissie voor de Geologische Kaart van Nederland, Koninklijke Vlaamse Academie voor Wetenschappen, Letteren en Schone Kunsten van België Klasse der Letteren. 1757. *Verhandelingen Uitgegeven door de Hollandsche Maatschappij der Wetenschappen*. Haarlem: Kruseman, pp. 502-503.
- Hallett, A. F., Isaäcson, M. and Meyer K. F. 1973. Pathogenicity and immunogenic efficacy of a live attenuated plague vaccine in Vervet monkeys. *Infection and Immunity*. 8(6): 876-881.
- Hirschhorn, L. R., Ojikutu, B. and Rodriguez, W. 2007. Research for change: Using implementation research to strengthen HIV care and treatment scale-up in resource-limited settings. *Journal of Infectious Diseases*. 196(Suppl. 3): S516-S522.
- Horton, R. 2000. After Bezwoda. *Lancet*. 355(9208): 942-943.

Irwin, L. 2006. Keynote address: Is evidence overrated? *Proc. International Symposium on the Nature, Purposes, Ethics and Politics of Evidence in a Democracy. Academy of Science of South Africa, September.* p. 11.

Isaakidis, P., Swinger, G. H., Pienaar, E., Volmink J. and Ioannidis, J. P. A. 2002. Relation between burden of disease and randomised evidence in sub-Saharan Africa: Survey of research. *British Medical Journal.* 324: 702-704.

Jochelson, K. 1999. Sexually transmitted diseases in nineteenth and twentieth century South Africa. In: P. Setel, M. J. Lewis, M. Lewis and M. Lyons (Eds.) *Histories of Sexually Transmitted Diseases and HIV/AIDS in sub-Saharan Africa*, Santa Barbara. US: Greenwood Publishing Group, p. 225-230.

Katz, E. 1995. *The White Death: Silicosis on the Witwatersrand Gold Mines, 1886-1910.* Johannesburg: Witwatersrand University Press.

Kazanjian, P. 2004. Changing interest among physicians toward pneumococcal vaccination throughout the twentieth century. *Journal of the History of Medicine and Allied Sciences.* 59(4): 560.

Logan, C. 2003. *Celebrity surgeon: Chris Barnard, a Life.* Cape Town: Jonathan Ball. pp. 103, 113, 146.

Louw, J. H. 1969. In *the Shadow of Table Mountain: A History of the University of Cape Town Medical School.* Cape Town: Struik. pp. 137, 398, 400.

Malan, M. 1988. *The Quest of Health: The South African Institute for Medical Research, 1912-1973.* Johannesburg: Lowry Publishers. p. 142, 305, 293-297.

Marasas W. F. O. 1988. Fungal toxins: A hidden menace in foodstuffs. In: A. J. Brink (Ed.), *South African Medical Research: Twenty Years of Growth.* Pinewood: Owen Burgess. pp. 41-45.

Marks, S. 1997. Public health then and now: South Africa's early experiment in social medicine: Its pioneers and politics. *American Journal of Public Health.* 87(3): 452-459.

McCulloch, J. 2005. Beating the odds: The quest for justice by South African asbestos mining communities. *Review of African Political Economy.* 32(103): 63-77.

Meiring-Naudé, S. and Brown, A. C. 1977. The growth of scientific institutions in South Africa. In: A. C. Brown (Ed.), *A History of Scientific Endeavour in South Africa.* Cape Town, Royal Society of South Africa: Rustica Press. pp. 60-85.

Metz, J. 1988. James Gear (1905-). In: A. J. Brink (Ed.), *South African Medical Research: Twenty Years of Growth.* Pinetown: Owen Burgess. pp.19-20.

Myers, J. 2006. The business of health, the health of business. *South African Medical Journal.* 96(11): 1174.

National Health Research Database (NHRD). Available at: <http://www.researchdatabase.org.za>.

- Nattrass, N. 2006. *Mortal Combat: AIDS Denialism and the Struggle for Antiretrovirals in South Africa*. Pietermaritzburg: University of KwaZulu-Natal Press.
- Niewijk, A. 1999. Tough priorities: Organ triage and the legacy of apartheid. *The Hastings Center Report*. 29(6): 42-50.
- Packard, R. M. 1987. Tuberculosis and the development of industrial health policies on the Witwatersrand, 1902-1932. *Journal of Southern African Studies*. 13(2): 187-209.
- Packard, R. M. 1989. *White Plague, Black Labour: Tuberculosis and the Political Economy of Health and Disease in South Africa*. Pietermaritzburg: University of Natal Press.
- Packard, R. M. 1993. The invention of the 'tropical worker': Medical research and the quest for Central African labour on the South African gold mines, 1903-36. *The Journal of African History*. 34(2): 271-292.
- Palladino, P. and Worboys, M. 1993. Science and imperialism. *Isis*. 84(1): 91-102.
- Peltzer, K. 2008. Use of traditional complementary and alternative medicine for HIV patients in KwaZulu-Natal, South Africa. *BMC Public Health*. 8(1): 255.
- Pienaar, E. D., Volmink, J., Zwarenstein, M. and Swingler, G. H. 2002. Randomised trials in the South African Medical Journal, 1948-1997. *South African Medical Journal*. 92(11): 901-903.
- Price, C. H. 1959. *Diary of Dr. Mackrill, Africana Notes and News*. 13(8): 314-16; also T. James, Sieketroot; and N. Mathie, *Man of Many Facets: Atherstone, Dr. W. G.* in 3 volumes, published by the author, 1997-8. Vol.2, pp. 472-74.
- Quarterly Bulletin of the SA Library. 1969. An American girl at the Cape in 1834 (reprint). 23(3): 83-96.
- Rosendorff, C. 1988. Dynamics of blood flow. In: A. J. Brink (Ed.) *South African Medical Research: Twenty Years of Growth*. Pinetown: Owen Burgess. pp. 203-207.
- Sandler, E. M. 1974. Lichtenstein's vaccination tour – 1805. *Supplement to the South African Medical Journal*, 48.
- Schonland, B. 2005. Cited in D. Walwyn. *Serving the needs of society with revolutionary bioscience research*. Pretoria: CSIR. p. 4.
- Schoub, B. D. 2003. Director's report, National Institute for Communicable Diseases (NICD), Annual Report 2003.
- Schutte, C. H. J., Jackson, T. F. H. C., Pammenter, M. D. and Sharp, B. L. 1988. The fight against infection. In: A. J. Brink (Ed.), *South African Medical Research: Twenty Years of Growth*. Pinetown: Owen Burgess. pp. 21-30.
- Sidley, P. 2000. South Africa to tighten control on drug trials after five deaths. *British Medical Journal*. 320: 1028.
- South African AIDS Vaccine Initiative (SAAVI). Available at: <http://www.saavi.org.za/index.htm>.
- Spinage, C. A. 2003. *Cattle Plague: A History*. London: Springer; see also T. D. Brock. 1999. *Robert Koch: A Life in Medicine and Bacteriology*. American Society for Microbiology, ASM Press.

- Stepan, N. 1982. *The Idea of Race in Science, Great Britain 1800–1960*. London: Macmillan. p. 172.
- Steyn, N. P., Bradshaw, D., Norman, R., Joubert, J. D., Schneider, M. and Steyn, K. 2006. *Dietary Changes and the Health Transition in South Africa: Implications for Health Policy*. Cape Town: South African Medical Research Council. pp. 34-35.
- Sutton, G. 2004. *James Lind aboard Salisbury*. The James Lind Library. Available at: <http://www.jameslindlibrary.org>.
- Swanson, M. 1977. *The Sanitation Syndrome: Bubonic plague and urban native policy in the Cape Colony, 1900–1909*. *Journal of African History*. 18(3): 387-410; see also Swanson, M. J. 1983, *The Asiatic Menace: Creating segregation in Durban 1870–1900*. 1983. *International Journal of African Historical Studies*. 16(3):401-421.
- Tröhler, U. 2000. *To improve the evidence of medicine: The 18th century British origins of a critical approach*. Edinburgh: Royal College of Physicians.
- Tucker, T. J. and Makgoba, W. M. 2008. *Public-private partnerships and scientific imperialism*. *Science*. 320(5879): 1016-1017.
- Van Heyningen, E. 1984. *The social evil in the Cape Colony 1868–1902: Prostitution and the Contagious Diseases Acts*. *Journal of Southern African Studies*, 10(2): 170-197.
- Vaughan, C. L. 2008. *Imagining the Elephant: A Biography of Allan MacLeod Cormack*. Cape Town, UCT Press.
- Volmink, J. 2005. *Addressing inequalities in research capacity in Africa*. *British Medical Journal*, 331: 705-706.
- Volmink, J. 2008. *The willow as a Hottentot (Khoikhoi) remedy for rheumatic fever*. *Journal of the Royal Society of Medicine*. 101: 321-323.
- Wreford, J. 2006. *Facilitating relationships between African traditional healing and Western medicine in South Africa in the time of AIDS: A case study from the Western Cape*. Cape Town, UCT, The Centre for Social Science Research (CSSR) Working Paper No. 170.
- Wylie, D. 2001. *Starving on a Full Stomach: Hunger and the Triumph of Cultural Racism in Modern South Africa*. London and Charlottesville: University Press of Virginia, p. 127-160.
- Youde, J. R. 2007. *AIDS, South Africa, and the politics of knowledge*. Farnham, UK: Ashgate Publishing.

CHAPTER 3:

DEVELOPING A NATIONAL CULTURE THAT IS SUPPORTIVE OF
CLINICAL RESEARCH, AND AN AGENDA FOR CHANGE

In this chapter, we engage with the following questions:

1. What is a national culture that is supportive of good clinical research?
2. What principal components make up a productive national culture supportive of good clinical research?
3. What is the status of clinical research in the country?

DEFINITIONS

There are many difficulties in the notion of a 'national culture', a term which means many different things to different people and communities. We will use the term in this report as connoting **generally accepted patterns of thinking or acting that are relatively stable over time**, and have some sectoral or functional specificity or scope. Because we are ultimately dealing with a summative 'national culture', each specific domain is to some extent nested within a bigger one. This can be readily seen when one considers the domain of clinical research (with its particular complement of active and trainee researchers, direct partners such as funders and institutions, and other stakeholders, regulators who scrutinise and approve their projects, and sponsors and funders who make their work possible), and extends this to the much larger domain of the citizenry at large, for each of whom clinical research is a field that potentially impinges on a vital interest, namely good health and longevity for self, family and community. Layered between these core and macro domains are further sectors of relevant business and industry, government policy-making, systemic health care provision, and the like.

A particular 'culture' might mean that one or the other contrasting standpoints is embraced by the majority of participants in the sector concerned. Wise and effective policy-making requires that both well-based **minority opinions** and generally held **majority opinions** be taken into account. In the case of the research sector itself, the establishment of a national association for clinical research might permit evidence-based harmonisation of such positions

through round-table discussions or task teams, while at the level of the broad public particular methods might be followed. An example of the latter are the expert panels in the UK which engage with randomly selected members of the public in television programmes, and in invited correspondence with all comers, including representatives of vociferous and/or opinionated minorities.

DEVELOPING A PRODUCTIVE CULTURE OF CLINICAL RESEARCH

We must assume that the researchers, the hospitals and clinics where the research is done, the regulatory bodies and funders are all uniformly in favour of a system of clinical research that will improve health care to the greatest possible extent, in a cost-effective, sustainable and equitable manner.

In this report we have identified **six principal components that make up a common, productive 'culture'** that is highly promotive of research that is high quality, wide and relevant in scope, beneficial to translational outcomes, and sustainable in the clinical sector. These are:

1. The acceptance of the principle that 'the proper study of humankind is humans themselves';
2. The understanding that sustainable health care systems require guidance by a critical mass of research-experienced clinicians and the continuous training of new generations of research-informed clinical care givers;
3. Recognition of the complex, multi-dimensional, and challenging nature of clinical research;
4. An appropriate balance between risks and benefits;
5. An appropriate balance between curiosity-driven and problem-directed research;

6. A clear emphasis on public service and public benefit;
7. Protection and development of new intellectual property.

We start by returning to the first, narrowly-focused question posed above. In words that are slightly altered from the cited original propositions, is the '**proper science and study of humankind, humans themselves**'? (Pope, 1733.) Many years of reductionism in health sciences have revealed countless instances where assumptions of equivalence between humans and laboratory mammals such as rats, mice and primates of various kinds have proved to be incorrect (Casanova and Abel, 2007). A good example is in the complex field of clinical immunology, where detailed studies of genetic immunopathies in human participants have consistently shown the risks of assuming that information gleaned from mice is necessarily applicable to humans (Schnabel, 2008). Some models of human diseases have been deliberately engineered in laboratory animals (Peh *et al.*, 2002; Wine *et al.*, 2002; Itoh and Narushima, 2005; Aliev and Burnstock, 1998; Lieschke and Currie, 2007), and much drug testing is conducted on selected animal species. In most cases, the validity of the reductionistic or comparative models has proved problematic, even if much useful knowledge has been generated that has made the design of human studies simpler, less open-ended and more focused. It seems, nevertheless, that in general only studies of humans can yield a true picture of human disorders, especially because this generalisation is in any case itself subject to the enormous genotypic and phenotypic variation that is present in the human species itself.

A second aspect of the sectoral 'culture' is the belief that a **cadre of research-experienced clinicians** is essential in the health care system for well-informed, direct health care provision, for the **teaching and training of succeeding generations of practitioners**, and for the design of health care systems that provide best-possible preventive and therapeutic health care to both individuals and populations (this applies to the deeply established health 'cultures' in India and China as much as it applies to the prevailing and much more recent 'Western' model).

A third, narrowly focused 'cultural' issue concerning clinical research is its **cost and multi-dimensional complexity** compared with studies that are purely laboratory based, which is the main reason why animal and *in vitro* studies still vastly predominate in the broad health research area. Clinical researchers have to provide clinical service in order to underpin their investigative skills. Their involvement in patient care and also frequently in the training of new clinicians makes heavy time demands. The research itself requires theoretical and conceptual knowledge that is difficult to acquire, and even more difficult to maintain. The costs of subject hospitalisation or recruitment, frequently repeated special investigations, multiple subject work-up and skilled monitoring are often so high that grants have to be much larger than for other types of research. Meeting regulatory requirements makes demands on time and patience not found in other areas. Teams of diversely skilled researchers have often to be put together and managed in order to address different dimensions of clinical problems, with appropriate risk management. Simply put, clinical researchers, who must frequently also have access to the same kind of expensive equipment and consumables used by laboratory-based researchers, require a great deal of courage, resilience and energy, and must make a considerable, concerted effort on a variety of fronts. It is part of a certain 'culture' in which this kind of uphill research activity is valued, supported and deliberately fostered; it is easy to regard it in another 'culture' as 'causing too much trouble and cost'.

The fourth important 'cultural' issue in the sector is the **balance of risks and benefits**. Clinical research is unique in its interfaces, firstly with human rights and secondly with risk analysis. In both areas, certain kinds of 'cultures' can create significant impediments to the conception and execution of research projects and programmes, while others can have facilitatory and enhancing effects. Because of the element of novelty and uncertainty, there is a popular perception that clinical trials are more risky than everyday activities, while in fact this is not the case. A more precise adjustment of risks to benefits can bring about a prevailing 'culture' that promotes both clinical research and its positive impacts on the health of the population.

The fifth, often controversial consideration is **context and relevance**, which amounts in practice to translational purpose. It is possible in a particular culture to consider clinical science to be part of the 'blue sky' search for knowledge which sometimes 'spins off' benefits as serendipitous outcomes. An alternative culture seeks out topics that are obviously related to major health problems, and addresses them according to deliberate project designs, usually with carefully assembled multidisciplinary teams, to maximise the probability of beneficial public outcomes, and to underpin the attainment of those benefits in evidence-based ways. A balance between these polar opposites must be found in a resource-constrained system.

An overridingly important 'cultural' issue that directly affects the sector is motivation in respect of private as opposed to **public benefit**. Compared with a systemic prevalence of public-sector clinical research projects which are initiated and funded only in support of profits by pharmaceutical companies, and/or one where researchers are mainly hunting for personal glory and/or tangible benefits such as salary supplements, conference travel and other perks, the widespread existence of an ethos of public service and public benefit undoubtedly represents a desirable and necessary 'cultural' polarisation.

The last, but by no means least, of the dominant issues in a national culture supporting good clinical research concerns the imperative to protect and develop new discoveries in an efficient and effective intellectual property rights regimen that can bring benefits to both the health care practice and economic development of the country. This implies careful construction of partnerships, adequate funding of patent registration applications, and a tax system that incentivises innovation. It is a mind set as much as a regulatory approach.

THE PRESENT SITUATION

While there appears to be a broad acceptance of the need for studies on humans of human disease mechanisms and treatment and prevention strategies, the extensive domain of animal-based and *in vitro* studies (usually

intensively motivated for funding and support because of their relevance to human diseases), is not closely linked to the domain of clinical studies, organisationally or functionally. Clinical specialities, and in some cases even sub-specialities, have tended to withdraw into individual, small, internally interactive domains with their own national societies, conferences and periodicals or newsletters. Their better-quality publications have overwhelmingly appeared in international speciality journals indexed in the Thomson Reuters ISI Web of Science (ISI) system, something which in itself is a laudable aim and part of the national policy of 'internationalising' South African research. Unfortunately, it makes much of this good work effectively invisible to South African colleagues in other specialities, or to the non-clinical, laboratory researchers in the same or related fields (see Chapter 6 for details).

There is thus a distinct **lack of cross-fertilisation, peer consultation and functional community** in the local clinical research domain, which minimises the value of animal or *in vitro* models to the understanding of human diseases, and results in distrust and lack of communication between those who perform clinical studies and those who work reductionistically in laboratories. As the latter often have significantly more time to devote to their research activity, and can more readily assemble teams of associate scientists, graduate students and postdoctoral fellows, a sense of inferiority on the part of clinical researchers readily develops, which often leads to resentful closure of the few communication channels that do exist.

Ultimately, the deeper meaning of 'the proper study of humankind is humans themselves' is not compatible with a real or perceived position of clinical research as intellectually or methodologically second rate, compared with laboratory studies.

The **specific training and mentoring** required to capacitate researchers who are fully equipped to carry out studies on humans is mostly inadequate compared with that for laboratory investigators. This may or may not be due to significant extra costs and a lack of willing trainees, but it may also be symptomatic of a reluctance to embrace the principle of human studies

as core to human health. What is visible and highly problematic is a virtual absence of 'MD: PhD' programmes at the health science faculties, the lack of facilitation of participation of professional graduates in post-basic research honours and master's degree programmes through appropriate bursaries, career structures and organisational arrangements, and the paucity of centres of excellence and research chairs in this field (see below in this chapter and elsewhere in this report).

Research centres and institutions in developed countries have an enormous depth of human and other resources, augmented by easy communication and the willingness to put research at the top of priority lists. The **teaching and service loads** of clinical academics are very much lower than is the case for their counterparts in developing countries such as South Africa. Establishing and maintaining a critical mass of actively researching clinicians is accordingly extremely difficult in our situation, with emigration to greener fields in the North an ever-present temptation. It is thus understandable that the managers of health science faculties and the budget-challenged providers of health services have drifted to a model where the outcomes of clinical research performed elsewhere are incorporated into teaching and practice locally as far as that is possible, and truly **investigative clinical research is 'given up' as too costly, too difficult and too frustrating**. Sponsored 'me too' clinical trials and low-level 'action research' in pressurised clinical practice is often all that remains, presented to the world and society as relevant activity and appropriate to local conditions. But this kind of clinical research is not what is needed to promote best-possible health care and the most effective training and education of young clinicians, nor is it anything more than the acceptance of a kind of permanent 'colonial status' vis-à-vis the developed countries of the North.

It is symptomatic of the 'giving up' culture described above in relation to clinical research that the kinds of opportunities recently created for talented researchers in other fields by the Department of Science and Technology (DST) and the National Research Foundation (NRF) have not targeted the area of clinical research more than tangentially. The schemes for nationally selected

research chairs and centres of excellence, equipment catch-up programmes, and a national 'PhD project' have been enthusiastically implemented in non-clinical areas, and the MRC has been unable or unwilling to resolve the long-standing issue of its relationship to the strategic efforts of the DST (and cabinet) to strengthen R&D in the country. The fact is that **no programme exists that is designed to boost high-quality activity in clinical research as one of the country's most important intellectual spheres, specifically one which also promotes better designed and delivered health care, enhances foreign direct investment, and has been a traditional strength in the national system of innovation.**

Another demonstration of the 'giving up' culture pervading clinical research is the inexplicable neglect of an issue that has for years been the 'elephant in the room' in terms of **the organisational/operational context of the discipline.** With academic hospitals regarding research activity as outside their mandate, mission and brief, with the National Health Laboratory Service (NHLS) considering clinical research activity as a market like any other, and with the MRC intimating to clinical researchers that because of funding limitations it is unable to fund patient-related costs of otherwise supported projects, a huge gap appeared that no policy-making has addressed and no stakeholder or participant has clearly and publicly recognised and decried. The pharmaceutical industry has simply had to fill that gap by default (see other sections of this report). The public service ethos of this research domain has quietly declined, and curiosity-driven investigation has diminished.

The above situation is not compatible with the previously listed six core components of a productive, self-perpetuating national culture of high-quality clinical research. These components are inter-dependent, and operationalising them will require **concerted and cooperative actions by many of the stakeholders in central and provincial government.** The revitalisation and repositioning of clinical research in South Africa can help to develop new or more effective treatments for the health problems affecting our population. Creating a solid and efficient infrastructure for clinical research in South Africa can help to attract foreign direct investment for local economic

development, and developing and nurturing local clinical researchers can help to grow our human capital and reposition South Africa as a knowledge-based economy.

AN AGENDA FOR REVITALISING CLINICAL RESEARCH

The agents that determine the sectoral 'culture' in which clinical research can flourish through the above drivers are clearly multiple, interactively related and require joint action by direct and indirect funders of research (funding agencies and the National Treasury), by trainers and educators in the broad health domain (through career development approaches, curricula and coordinated planning), by hospital managers (in respect of cost containment), by external partners such as the NHLS through discounted fees, and by the policy-making environment (especially in the national Department of Health and the provincial health departments).

An expanded and adequately funded public sector involvement in clinical research, specifically in clinical trials, should meet the following expectations: (i) it would need to draw on the collective expertise and available competence, which is considerable; (ii) it should meet the national need in the public sector, including HIV/AIDS, tuberculosis, especially the drug-resistant forms, cancer, diabetes mellitus, diarrhoeal diseases and meningitis, among others; (iii) it should be non-profit in the sense that all or most profits would be ploughed back into research; and (iv) all activities would be contracted and pursued in a spirit of scientific excellence. The focus would be on what can be done uniquely, generally to avoid involvement in what others are capable of doing well and wish to do, which should be left to them.

Nonetheless, even with the above constraints, there is potential to work to be done in Phases I to IV clinical trials and in post-marketing surveillance, which has become increasingly important and has expanded beyond the strict confines of medicines and vaccines safety. The work may deal with special issues, including traditional medicines and pharmaco-economics (the latter is an especially important and neglected area in South Africa). Training would be at the heart of clinical research.

Much of the rest of this report expands on the high-level positions the Panel has taken on the narrow-focus, sectoral aspects of a national culture, “in which clinical research is seen as essential, and clinical trials are widely accepted and promoted as the most reliable basis for establishing the efficacy and safety of new therapies and approaches.”

NATIONAL CULTURE

First, we need to develop a national culture supportive of clinical research. The achievement of a strong ‘**public service and benefit**’ **ethos** is an absolute requirement for a sustainably excellent clinical research community. This does not exclude the recognition of fine personal or team contributions, nor of the recruitment of private-sector funding and partnership, nor of sponsored conferences and helpful equipment grants, etc. The explicit primary values of public service and benefit should simply pervasively and effectively inform the basic system of how clinical research is initiated, regulated, funded, reported and translated into improved health care of individuals and populations. Doing this would in itself provide regulatory mechanisms to harness the goodwill and resources of all the necessary partners in the enterprise.

Although general science promotion has been well funded, there are no government programmes currently promoting clinical research; greater attention has been paid to the basic sciences than the clinical sciences. There is no professional body or journal solely dedicated to the promotion of clinical research, and more local clinical researchers are publishing in specialist international journals. Campaigns to improve public engagement with science tend not to include clinical medicine.

The application of **realistic risk management** to clinical research will require critical analyses which can probe this topic in comparative terms throughout society, which can properly calculate and record risks against likely benefits, and, most important, which can train researchers to include such features in their proposals and to clarify aspects of the ethical design of their protocols. Linking this to efforts to improve the **public understanding of, and engagement**

with, clinical science will be most valuable. The research community itself must be responsible for enhancing the translational aspect of their project designs, in concert with appropriately modified guidelines for funding and partnerships that will bring the necessary skills into play.

Developing a national culture supportive of clinical research includes getting more public support for and participation in research. Public concerns about clinical research may impede recruitment to research, affect adherence to interventions and even threaten the continuation of research projects (Geissler, 2005; Molyneux, *et al.* 2005; Pool and Geissler, 2005; Fairhead *et al.*, 2006; Nchito, *et al.* 2003; Singh and Mills, 2005; Molyneux *et al.*, 2004). Such concerns may also affect recruitment to clinical research careers. Geissler and Pool (2006) suggest that rumours about clinical researchers engaging in blood and organ trafficking, deliberate spreading of disease and surreptitious birth control are widespread across Africa and pose a potential threat to public support of and participation in clinical research. Too little attention has been paid to understanding and improving public understanding of clinical research in South Africa. To do this we have to understand the legacy of the historically close relationship between clinical research agendas, the needs of industry and the colonial and apartheid state.

REGULATION

Second, there is a need for better capacitation of the ethics and regulatory bodies for clinical research. South Africa has a well-established ethics governance and regulatory environment, but this is currently decentralised, understaffed and underfunded, resulting in delays in the approval of clinical research protocols and a shortage of ongoing monitoring activities to ensure compliance with approved protocols. There has been an increase in overall workload, but a decline in industry-related clinical trials reviewed by research ethics committees (RECs) at South African academic institutions in recent years (Cleaton-Jones and Voster, 2008; Dhai, 2005). This illustrates the shift of clinical trials from academic institutions to the private sector, where trials are often less well regulated. Successful implementation of the new Intellectual Property Rights Act will require optimal alignment between this and the ethics-regulatory systems (see Chapters 5 and 9).

PUBLISHING

Third, concerted government and professional attention needs to be paid to the development of scientific publishing in clinical research and the development of an interdisciplinary local scientific community. Although South African researchers historically performed well on the international stage, there has been a decline in the number of ISI-listed journal articles in clinical medicine: from 1 063 publications in 1987 to 736 in 2001. This has represented a decline in South Africa's world share of publications in clinical medicine - for example, South Africa's share of the world's ISI-listed publications in clinical medicine declined by 18% from 0.59% (1990-1994) to 0.46% (1996-2000) (Pouris, 2003). It has also represented a decline in the proportion of local research in the field of clinical medicine from a 22 to 20% share of overall production (South African Department of Science and Technology, 2005). This problem is likely to increase as the proportion of older authors has been rising. For the period 2001 to 2006, 13% of all South African authors publishing in clinical science journals were over the age of 60. The ageing of authors in clinical research testifies to the shrinking of the health research workforce (see Chapter 6).

EDUCATION

Fourth, research institutions need to be supported in educating researchers and encouraging research outputs. Research experience and knowledge must be infused into undergraduate clinical education and training for this to be a basis of life-long learning and effective practice and service. At postgraduate level, this is the case to an even greater extent, yet opportunities for research and exposure to clinical researchers have diminished progressively over recent years in the face of huge service challenges and cutbacks in staffing and resources. A growing division of focus and responsibilities between health service organisations, on the one hand, and academic institutions and funding agencies, on the other, has largely severed the critical connection between research/scholarship and education/training. Prospective clinical researchers in South Africa have few focused training programmes and career paths, little in the way of appropriate facilities, and once qualified, lack a supportive

infrastructure to undertake patient-orientated clinical research or a career structure to support their progress as clinical scientists.

Specific measures need to be taken to ensure equity in research development. South Africa has not fully reversed the historical legacy of race and gender discrimination in clinical medicine or the institutional and regional imbalances in research capacity inherited from the past. Although more female and black authors have been publishing in the clinical medicine field than before, we have not yet reached race or gender equity in terms of publication outputs and clinician-researcher demographics. Most publications still come out of a few major South African universities which have developed a strong scientific base over the last century. A handful of researchers from a few main centres also conduct most clinical trials (see Chapter 7).

FUNDING

Fifth, there is need for better and more efficient funding of clinical research. Clinical research is currently being hampered by inadequate, uncoordinated funding, inadequate support from government health authorities, and lack of centralised research policy and management. Clinical research has experienced significant disinvestment since the 1980s because of the shift towards funding delivery of public health services in provincial hospitals, the loss of research subsidies from the NHLS and the lack of dedicated funding for clinical research. The MRC has failed to step up funding for clinical research in the face of withdrawal of funding by the provincial departments of health and the NHLS. Until now, despite its mandate to support all scientific research, the NRF has not directly funded clinical research. It has recently indicated a willingness to consider doing so. Much of the clinical and epidemiological research now being performed in South Africa is funded by foreign, non-private foundations and government bodies and not by private companies (see Chapter 8).

COORDINATION

Sixth, there is need for a concerted and coordinated effort by government, industry and research institutions to promote and develop clinical sciences. Creating an attractive environment to conduct clinical trials in this country requires better coordination and integration of different components of the system. In particular, there is a need for better coordination of government departments responsible for aspects of the revitalisation of clinical research. The DTI has an interest in attracting foreign direct investment by maximising and optimising the opportunities for multi-national research investment. At the same time, they wish to promote the growth of an indigenous biotechnology industry which has the capacity to create new therapies and to test them through appropriate clinical trials. The South African Government has identified the pharmaceutical industry as a priority industry to fuel economic growth under AsgiSA. Research is essential for growth in any industry, and clinical research is the lifeblood of a research-based pharmaceutical industry. The clinical trials industry is growing worldwide, and is seeking new locations for trials, so we compete for clinical trials with many other countries.

Science, technology and innovation are a key component of the NEPAD strategy for addressing the Millennium Development Goals (NEPAD, 2006), and research universities are being set up across Africa to promote postgraduate science. In 1996, the then South African Deputy President Thabo Mbeki envisaged a key role for science and technology in aiding the intellectual and spiritual renewal of Africa – the *African Renaissance*. The DST's Ten-Year Innovation Plan (2008) sets out to develop a knowledge-based economy in which the production and dissemination of knowledge leads to economic benefits and enriches all fields of human endeavour. It has to promote research and innovation in this highly inter-dependent and complex system, but this is dependent on the development of a skills base. Yet of the 72 NRF Research Chairs awarded to date, the majority of the (few) chairs awarded in the health sciences have supported basic rather than clinical sciences (NRF: <http://www.nrf.ac.za/sarchi/index.htm>).

The Department of Education (DoE - now the Department of Higher Education and Training, DoHET) has to make sure that the skills and capacities of health care personnel are developed to the highest degree possible, through the huge system of public higher education. Yet much of the teaching and research actually takes place problematically on the terrain of another ministry/department, namely that of Health, channelled just as problematically through provincial funding and responsibility. The DoH wishes to oversee an effective system of safety testing and approval of medicines and other therapies, and to ensure that these are affordable, safe and widely available; this requires that a research ethics and regulatory environment be created that is efficient and rational, capable of balancing interests, and trusted by all participants. Finally, the National Treasury has a deep interest in more efficient funding of health care, while providing for the education and training needs upon which health care delivery is critically dependent. Yet, as discussed above, there has effectively been massive disinvestment in clinical research since the 1980s.

There is a need for strategic servicing of clinical trials, and for expertise in their planning and budget, information technology support for trials, global biometrics, serious adverse event monitoring and reporting, training and retraining and perhaps certification, document management, and clinical study management. There would be opportunity to concentrate on niche areas such as Good Clinical Practice (GCP), biostatistics, data management support and the development of systems. New opportunities might be sought for collaboration between the private and public sectors, and for comprehensively addressing Good Laboratory Practice (GLP), GCP and quality assurance. In Malaysia at the University of Kuala Lumpur there is an institute for biochemistry and biometrics which serves as a national reference centre. One can take work there, offload work or data for processing, commission studies, and develop educational models and children's educational games. It is part of the national plan to promote mathematics, science and technology. It is open and used 24 hours, seven days a week. This is what should be done in South Africa in the area of public sector clinical studies.

There are problems, however, and there will be no success unless they are confronted. Activities must be confined to true science and clinical research; promotional studies must be avoided; there should be enlightened approaches to budgeting and costing; there will be ownership issues, including intellectual property of communities; there are limits to clinical trial capacity in the country; excellent systems of data management need to be put in place; this work can only be managed with reform of the national medicines regulatory process; there is a need for assessment tools for clinical trials capacity; insurance of patients has to be put in place, including no-fault liability; policies are needed regarding institutional overheads; and a business and funding plan is necessary.

If we are able to meet these challenges and plan strategically to revitalise clinical research, this is likely to benefit the African continent at large as well as South Africa.

FINDINGS

A national culture supporting clinical research will:

1. Accept the value of clinical research, based on the principle that ‘the proper study of humankind is humans themselves’;
2. Understand that sustainable health care systems require guidance by a critical mass of research-experienced clinicians and the continuous training of new generations of research-informed clinical caregivers;
3. Recognise the importance of investment in clinical research, due to its complex and multi-dimensional nature;
4. Enable an appropriate balance between risks and benefits in clinical research, ensuring ethical practice;
5. Enable an appropriate balance between curiosity-driven and problem-directed research in addressing key health risks in society;

6. Place clear emphasis on public service and public benefit in the conduct of clinical research, promoting public trust in and understanding of the role and contribution of research in society.

RECOMMENDATIONS

Develop a national culture supportive of clinical research by:

1. Raising the status of clinical research both within the broader domain of scientific research and within government programmes funding science;
2. Creating a strong public service and benefit ethos, based on better programmes promoting public engagement with clinical science, and better risk-benefit analyses that inform prioritisation for clinical research in the country;
3. Capacitating local ethics and regulatory bodies for clinical research;
4. Developing an interdisciplinary local scientific community through scientific publishing and coordinated promotion activities, while encouraging links between laboratory-based and clinical research;
5. Enhancing specialist knowledge and competence that is internationally visible, without reducing interdisciplinary communication among clinical researchers within South Africa;
6. Creating targeted educational programmes, funding, career-pathing and institutional support for the development of new clinical researchers in the country;
7. Increasing and better coordinating the funding of clinical research;
8. Working towards a concerted and coordinated effort by government, industry and research institutions to promote and develop clinical research capacity at the highest level possible.

REFERENCES FOR CHAPTER 3

- Aliev, G. and Burnstock, G. 1998. Watanabe rabbits with heritable hypercholesterolaemia: A model of atherosclerosis. *Histology & Histopathology*. 13: 797-816.
- Casanova, J. L. and Abel, L. 2007. Primary immunodeficiencies: A field in its infancy. *Science*. 317: 617-619.
- Cleaton-Jones, P. and Voster, M. 2008. Workload of a South African health research ethics committee in 2003 and 2007. (Unpublished report).
- Department of Science and Technology (South Africa). 2008. Ten Year Innovation Plan. Available at: <http://www.dst.gov.za/publications-policies/strategies-reports>.
- Dhai, A. 2005. Research ethics review – Protecting participants in research. *South African Medical Journal*. 95(8): 595-597.
- Fairhead, J., Leach, M. and Small, M. 2006. Public engagement with science? Local understandings of a vaccine trial in The Gambia. *Journal of Biosocial Science*. 38: 103-116.
- Geissler, P. W. 2005. Kachinja are coming! Encounters around a medical research project in a Kenyan village. *Africa*. 75: 173-202.
- Geissler, P. W. and Pool, R. 2006. Editorial: Popular concerns about medical research projects in sub-Saharan Africa – A critical voice in debates about medical research ethics. *Tropical Medicine and International Health*. 11: 7.
- Itoh, K. and Narushima, S. 2005. Intestinal flora of animal models of human diseases as an environmental factor. *Current Issues of Interest in Microbiology*. 6: 9-15.
- Lieschke, G. J. and Currie, P. D. 2007. Animal models of human disease: Zebrafish swims into view. *Nature Reviews Genetics*. 8: 353-367.
- Molyneux, C. S., Mutemi, W. and Marsh, K. 2005. Trust and informed consent: Insights from community members on the Kenyan coast. *Social Science & Medicine*. 61: 1463-1473.
- Molyneux, C. S., Peshua, N. and Marsha, K. 2004. Understanding of informed consent in a low-income setting: Three case studies from the Kenyan coast. *Social Science & Medicine*. 59: 2547-2559.
- Nchito, M. F., Geissler, P. W., Mubila, L., Friis, H. and Olsen, A. 2003. The effect of iron and multi-micronutrient supplementation on *Ascaris lumbricoides* reinfection among Zambian schoolchildren – A two by two factorial study. *Transactions of the Royal Society for Tropical Medicine and Hygiene*. 98: 218-227.
- NEPAD. 2006. African Science, Technology and Innovation Indicators: Towards African Indicator Manuals. A discussion document. Available at: http://www.nepadst.org/doclibrary/pdfs/iaatii_jun2006.pdf.
- Peh, W. L., Middleton, K., Christensen, N. et al. 2002. Life cycle heterogeneity in animal models of human papillomavirus-associated disease. *Journal of Virology*. 76: 10401-10416.
- Pool, R. and Geissler, P. W. 2005. *Medical Anthropology*. London: The Open University Press.

Pope, A. 1733. *An Essay on Man, Epistle 2*. London: J. Wilford. (Drawing on P. Charron. 1602. *De la Sagesse*, Book 1, Preface.)

Pouris, A. 2003. South Africa's research publication record: The last ten years. *South African Journal of Science*. 99: 425-428.

Schnabel, J. 2008. Neuroscience: Standard model. *Nature*. 454: 682-685.

Singh, J. A. and Mills, E. J. 2005. Cited in P. W. Geissler and R. Pool. 2006. Editorial: Popular concerns about medical research projects in sub-Saharan Africa – A critical voice in debates about medical research ethics. *Tropical Medicine and International Health*. 11: 7, 975.

South African National Research Foundation. Available at: <http://www.nrf.ac.za/sarchi/index.htm>.

Wine, J. J., Dean, M. and Glavac, D. 2002. Natural animal models of human genetic diseases. *Methods in Molecular Medicine*. 70: 31-46.

CHAPTER 4:

HOW TO FOSTER GREATER PUBLIC ENGAGEMENT WITH
CLINICAL SCIENCE

In this chapter, we engage with the following questions:

1. How can fostering better public engagement with science in general promote a national culture supporting clinical research?
2. What do we know about public opinion of clinical research in South Africa?
3. What can we do to improve public understanding of and trust in clinical research?

INTRODUCTION

As discussed in Chapters 2 and 3, **public understanding of medical research**, and science in general, has been negatively affected by our history of colonialism, 'Bantu' education and the continuing inadequacies of our science education system. Unfortunately, medical researchers have been slow to engage with South African communities to build public trust in clinical research, and where this engagement has happened it has been difficult and often unsuccessful. Fostering better public engagement with science can promote a national culture supporting clinical research. Fostering more effective interaction between scientists and the public about the aims, methods and findings of clinical research may also help to make clinical research more relevant, and more sensitive to the needs and perceptions of participant communities. Fostering better public understanding of and trust in the benefits of clinical research for society may improve willingness to participate in research, to recruit more young researchers to clinical research careers, and to support state funding of research.

Developing a national culture of support for clinical research depends not only on providing information to improve the public's general knowledge about science but also on increased mutual knowledge and trust between scientists and the public. **Public trust in medical science** can be hampered by ignorance about science 'from the inside' (how science works) and, perhaps

more seriously, by misunderstandings between scientists and the public about 'science from the outside'. Understanding 'science from the outside' includes understanding the role and value of scientific research, how it generates value for others and how it relates to other forms of knowledge: its place within the broader political economy of power, money and knowledge. Public mistrust of science may be associated with cultural and historical factors as well as the lack of specific scientific knowledge. Developing better communication and trust between scientists and the public should thus be based on a better understanding of how the public feel about science already.

PUBLIC UNDERSTANDING AND OPINION OF MEDICAL RESEARCH

Public perceptions of medical research and science in general will affect their participation in, and support of, clinical trials and clinical research. **Public confidence** in expressing opinions contrary to scientific views has strengthened in recent years. Disputes over scientific research in the public domain have become more frequent, for example on the question of scientific research on the human remains of indigenous people. The public has challenged the removal and 'ownership' of these remains by scientists, for example in the case of the Mapungubwe remains at Pretoria University and the Prestwich Place graveyard in Cape Town (Legassick, 2000; Shepherd, 2007). The media has also begun to play a greater role in influencing public perceptions of clinical trials. For example, in 2007 there was public outrage after an HIV microbicide trial was stopped in KwaZulu-Natal, "heightened by sensational media coverage depicting the women as 'guinea pigs', alleging that participants in microbicide trials were encouraged to visit bars and other similar places of entertainment, and engage in unprotected sex" (www.plusnews.org/Report.aspx?ReportId). The trial had passed all the relevant ethics approvals but had failed to achieve a sufficient level of public consultation and trust to deal with such a setback.

PUBLIC UNDERSTANDING OF SCIENCE

In spite of growing interest in the promotion of science, biotechnology research and community intellectual property protection, there has been too little research on the public understanding of science or on public perceptions of clinical trials in South Africa. The little research that has been done has been trapped to some extent in the '**knowledge deficit**' tradition, focusing on how little knowledge the public has about science. Instead of simply investigating public knowledge about science 'from the inside' (how science works to produce knowledge) we need to start investigating how people understand the purpose and politics of scientific research and how it affects them.

Current research understands poor public engagement with science in South Africa mainly as a problem of **poor communication** that can be addressed by telling people more about science, developing indigenous-language terminology, or phrasing sexual behaviour messages in a more culturally appropriate way. The problem could also, however, be seen as a **broader socio-political issue**, linked to a history of popular experience of science in South Africa, as elsewhere in Africa, that has resulted in a mismatch between popular and scientific understanding of the role and value of science in society.

In 1999, a survey was conducted by the HSRC to determine the level of public understanding of science in the country using modified international survey instruments (Blankley and Arnold, 2001). The data from the sample of 2 207 randomly selected adults were weighted to match the demographics of the national adult population. The data showed that 30% of respondents had never studied mathematics at school, 50% had never studied biological science and 55% had never studied physical or chemical science. Only about 20% had a pass in mathematics on leaving school and only 3% to 4% of the sample had ever studied mathematics or science at tertiary level. Race, age, gender and income level were correlated with levels of science or mathematics education: poorer, older black women were worst off.

Although the South African respondents showed interest in science (83% were interested in new discoveries in medicine), the study found that science was

a low-salience issue for most of them prior to the survey. Although 60% of the respondents believed that the positive benefits of science had outweighed any harmful effects, perhaps mirroring government statements on the usefulness of science, 68% felt that “science makes our way of life change too fast”, and 48% felt that “we depend too much on science and not enough on faith”. Analysis of the data suggested that there are some problems in applying a survey developed for wealthy western countries directly to South Africa: people who were most optimistic about its benefits also showed the most reservations about science, in contrast to US data. The authors of the study suggest this may have been a result of random or unconsidered survey responses, but it may be that different applications of science may present reasons for concern or optimism.

The HSRC study thus recommended more **investment in science education** especially for certain groups, and the use of radio programmes for science education among the general population (Blankley and Arnold, 2001). Public education could also be achieved through revision of school curricula, systematic use of popular science magazines and science centres for information dissemination, a National Health Research week and other initiatives discussed below. As the British experience has shown, however, simply disseminating knowledge about science will not necessarily foster trust in science or address all the concerns that the public might have about science and more specifically about clinical research. Blankley and Arnold (2001) warned that “Given current low levels of understanding [about science], there is the danger that **public debates** on issues such as HIV/AIDS, nuclear power or genetically modified organisms are likely to be guided, even swayed, by those with special interests or agendas.”

Studies of **school performance in science** indicate that the percentage of final-year school passes in mathematics and physical science higher grade have declined slightly in the period 1997–2000, while passes in the standard grade in these subjects have risen somewhat. The performance of African learners in these subjects has been particularly poor: in 2001, between 11% and 40% of candidates passed mathematics on SG or HG in the various provinces (an outlier being the 75% pass rate for Limpopo with 78 learners)

(Mouton *et al.*, 2002). Numbers of both master's and doctoral graduates have increased between 1989 and 2000, but the majority of graduates are still in the humanities rather than the sciences (Bunting, 2002 and Cloete *et al.*, 2002, cited in Mouton *et al.*, 2002).

A preliminary scoping study on the **uptake of research in social development** was recently commissioned by the Research and Development Uptake in South Africa (RADUSA) Forum, comprised of the NRF, the Southern African Research and Innovation Management Association (SARIMA), the CSIR, the Association of Commonwealth Universities (ACU) and Metalab. The report of this investigation, produced by the CSIR (Funke *et al.*, 2008), may have limited value in measuring efforts to disseminate medical research information because it did not incorporate specific interviews with the MRC. People from a number of other science councils, government departments, higher education institutions and communities were sampled, but there were a few comments made about public views on science, specifically health information. Information about water quality or sexual behaviour provided by government agencies in the rural area sampled was not always acceptable to or trusted by community members. Information about healthy eating was not always relevant when people struggled to find enough to eat. The report concluded that "Government agencies and research organisations should be aware that cultural and linguistic barriers exist when they attempt to disseminate research and development findings to communities in need. These issues need to be addressed on a project-specific basis, and might also make for important areas for future research" (Funke *et al.*, 2008).

PUBLIC PARTICIPATION IN CLINICAL TRIALS

One of the measures of public trust in medical research could be participation in clinical trials. Recruitment to clinical trials in Europe has been dropping, making it difficult to achieve full enrolment, even as people have become more educated about science (Smith, 2000; Williams *et al.*, 2008). One of the reasons why South Africa is advertised as an attractive location for clinical trials is that the country has a good clinical infrastructure, and a large urban

population who are apparently treatment-naïve and willing to participate (Scholtz and Pretorius 2005). **Recruitment for clinical trials** has been easier in South Africa in an environment of high unemployment and difficulty accessing expensive drugs, and perhaps also in an environment in which people have limited scientific literacy.

Buckley (2008) suggests several factors may have adversely “affected the public’s relationship with health care research in Europe and the US: increased data protection legislation and the resultant consent requirements; access to unforeseen levels of both information and misinformation through the mass media; and a growing culture of personal choice which may have eroded the perceived importance of activities whose benefits are societal rather than personal”. But in general there is little research on patients’ views about participation in clinical research (Lecouturier *et al.*, 2008). In the US, black participants and other minorities are under-represented in clinical trials. Some commentators have ascribed this to popular memory of the unethical Tuskegee syphilis trials (which were only stopped in 1972). However, others say that public concern about Tuskegee is simply presented an excuse for laziness in recruitment efforts by researchers among African Americans. Such efforts would involve public education to reduce broader distrust about the purpose of the research, especially if it involves genetic testing of black doctors in the study, making arrangements for travel and child care and so on (Editorial, 1997).

South Africa does not seem to have had high-profile ethical trial disasters like Tuskegee in the US, but there have been examples of **unethical medical research** in the country. These are, however, relatively poorly documented (*The Guardian* newspaper, 1998; Cohen, 1997; Smith and Nicodemus, 1999; Schoofs, 2001, cited in Barsdorf and Wassenaar, 2005). As has been mentioned in Chapter 3, the long history of state support for medical research, the historically mainly white and male composition of medical doctors and the often adversarial relationship between medicine and indigenous healing traditions must have influenced experiences and perceptions of medical research and willingness to participate in clinical trials (Baldwin-Ragaven,

De Gruchy and London, 1999). Lurie and Wolfe (1997) pointed out that some HIV trials in developing countries such as South Africa have been unethical because they offer a different standard of care to developing and developed country participants, but these kinds of inequalities may not be evident to local trial participants.

There has been an assumption that providing more information to communities about clinical trials, such as the AIDS vaccine trials, will promote faith in science and recruitment to clinical trials in South Africa. Swartz and Kagee (2006) suggest that empowering people to know more about the costs and benefits of trial participation may make them less likely to decide to participate in the trials. Greater knowledge of science may not by itself promote altruistic involvement in clinical research, or indeed trust in anonymous testing procedures. Quite apart from the ethical requirements for informed consent, **better-informed participants** may also be more likely to stay on a trial. Other factors such as perceived risk can also play a role in willingness to participate. In the HSRC/ Nelson Mandela HIV survey for 2005, male, Indian or white respondents were in fact more likely to refuse participation and testing than women, coloured or African respondents (30% of those interviewed refused HIV testing, but refusals were not evenly distributed across the sample). Those at higher risk of HIV infection were more likely to agree to being tested (Shisana *et al.*, 2005). In some situations, rural black communities have shown good knowledge of, and positive attitudes to, biomedical interventions such as vaccination, and a generally positive attitude to HIV vaccines and vaccine trials (Lindegger *et al.*, 2007).

Barsdorf and Wassenaar (2005) indicate that there are racial differences in public perceptions of voluntariness of trial participation. African Americans are less likely to participate in clinical research than white in the US (Fairchild and Bayer, 1999; Bull, 2003, cited in Barsdorf and Wassenaar, 2005), and recruitment of black participants in South African vaccine trials has also been problematic. In a sample of 111 employees from two urban communities in South Africa, Barsdorf and Wassenaar (2005) found that black respondents perceived participation in medical research to be less voluntary than white and Indian respondents, independent of educational level, knowledge of

medical research procedures and close or personal experience of medical research. Lower perceptions of voluntariness among black trial participants may be due to South Africa's racist past, and possibly to awareness of abuses of medical research which are often more frequent in research conducted on disadvantaged groups. It is not clear how perceived lack of voluntariness would necessarily lead to decreased participation, however – it may increase participation of vulnerable groups.

Public ambivalence towards trial participation is expressed in different ways depending on the cultural, historical and political context, but there are some broad commonalities across Africa. There are widespread bioethics discussions within the scientific community about 'guinea-pig' trials which do not benefit locals, and about lax ethical controls in Africa, for example (Humphreys, 2006; Bosch, 2004), but in the popular imagination these concerns are often expressed in the form of rumours about blood and organ trafficking, deliberate spreading of disease and surreptitious birth control (Geissler and Pool, 2006). Geissler and Pool suggest that such rumours are widespread across Africa. They impede recruitment to research, affect adherence to interventions and even threaten the continuation of whole research projects while more commonly providing a background noise without direct impact (Geissler, 2005; Fairhead *et al.*, 2006b; Nchito *et al.*, 2003; Singh and Mills, 2005: 975; Molyneux *et al.*, 2004). Similar patterns of public concern about western medicine surface in South Africa and affect clinical trials. In the 1960s, heart surgeons at Groote Schuur Hospital were thought to be harvesting organs from black people for use in white people (especially after Barnard failed to obtain permission from one donor's family before using the heart) (Digby, 2006: 368). Such rumours were common in the northern parts of South Africa in the early 1990s, linking popular fears about organs being stolen for *muti* medicine or witchcraft to fears of a new transplant market for organs in public hospitals (Niehaus, 1993; Champion-Vincent, 2002; Comaroff and Comaroff, 1999). As Scheper-Hughes (1996) points out, rumours about organ stealing have some metaphorical or actual truth, especially when the full extent of 'dirty tricks' campaigns in times of political oppression become known, where poor people's bodies are treated without much respect in public hospitals, where 'presumed consent' is common practice in organ harvesting from corpses, and the illegal market

in blood and organs. While rumours take the form of urban legends, they are not simply the product of ignorance or resistance, but “local interpretations of medical research ethics – especially relating to the problem of resource transfers and flows of value” (Geissler and Pool, 2006).

Public understanding of trials and their benefits is also informed by the fact that the **pharmaceutical industry** consists mainly of large companies whose head offices are located in wealthy Western countries, and that the benefits of trial participation do not always filter down to the communities involved. As Alfred Chandler (2005) says in his magisterial history of the American and European chemical and pharmaceutical industries, their emergence in the second phase of the industrial revolution from the 1880s was made possible by the development of infrastructure enabling mass production and distribution – the railroad and steamship, the telegraph and cable. Conditions in the newly unified Germany and the growth of heavy industry along the Rhine gave pharmaceutical companies there and in Switzerland particular advantages, which helped them to retain market dominance into the 20th century, while yielding a bit of ground to American pharmaceutical companies in terms of innovation after they entered the market in the 1920s and 1930s. The product-related embedded organisational knowledge base generated by these early American and European pharmaceutical and chemical companies effectively defined the industry and constituted a significant barrier to new entrants, even from countries like Japan. The pharmaceutical industry expanded after World War II with the development of antibiotics. In the 1970s, new areas of scientific investigation such as microbiology, enzymology, genetic engineering and genomics were taken up and exploited by the industry's leaders. With the emergence of the **biotechnology industry** in the late 20th century, significant shifts in the industry occurred and reduced some barriers to entry for biotechnology start-ups, but it has been difficult for companies in South Africa to override barriers to entry in the arena of mass drug production and therefore in the financing of clinical trials required for drug registration and approval.

Although clinical trials are essential in testing and approving new drugs, and have brought increased research income into South Africa especially in

recent years after regulations governing the location of trials were liberalised, the specific political and economic features of the pharmaceutical industry has raised valid questions about research capacity development, the development and monitoring of local ethical guidelines, data access and the relevance of research to the local context. Most of the leading scientists on clinical trials are located in wealthy countries. New drugs are often designed for developed-country markets, and may be too expensive or inappropriate for the developing countries in which they have been tested (Benatar, 2002). This means that by participating in such trials, local researchers can lose opportunities to develop locally relevant research (Mayosi, 2008). Tucker and Makgoba (2008) have suggested that more non-Africans than Africans still occupy decision-making positions in many public-private partnerships regulating what HIV/AIDS, malaria and TB trials will be conducted in Africa: this, they say, constitutes a continuation of the pattern of scientific imperialism that historically characterised the sector (Tucker and Makgoba, 2008). Much of the **intellectual property (IP)** and research experience generated by clinical trials is thus located outside of developing countries such as South Africa, and local access to drugs still under patent is limited by their greater cost.

CURRENT INITIATIVES TO PROMOTE CLINICAL SCIENCE IN SOUTH AFRICA

The state in South Africa has come to be viewed by a wide range of academics and policy-makers as a **developmental state** – one that actively intervenes in the economy to harness resources for economic development, especially in poor communities. It is often assumed that South Africa's transformation into a knowledge-based economy, as in Asia, will "largely be dependent on the existence of a developmental state that promotes technological innovation and takes measures to enhance the human capabilities of its people" (Edigheji, 2008). In 1996, the then Deputy President, Thabo Mbeki, envisaged a key role for science and technology in aiding the intellectual and spiritual renewal of Africa – the *African Renaissance*. As stated in Chapter 7, science, technology and innovation are a key component of the NEPAD strategy for addressing the **Millennium Development Goals** (NEPAD, 2006) and research universities are being set up across Africa to promote postgraduate science.

It is critical to develop a national culture in which both doctors and patients are able and willing to consider the results of clinical research in deciding on health care solutions. In South Africa, the NRF is already promoting public engagement with science. The **South African Agency for Science and Technology Advancement (SAASTA)**, an agency of the NRF, aims to advance public awareness, appreciation and engagement of science, engineering and technology in South Africa. It was formerly known as the Foundation for Education, Science and Technology (FEST), but changed its name when it was incorporated into the NRF in December 2002. Its scope of activities includes:

1. Building the quantity and quality of mathematics and science outputs at school level (developing science education and training (SET) human capital);
2. Raising the general interest in, engagement and appreciation of the public (and especially poorer communities) for the benefit of science (strengthening the SET culture);
3. Communicating science to the South African citizenry (bringing science and scientists closer to civil society) (<http://www.saasta.ac.za/aboutus/background.shtml>).

SAASTA hosted the first African Science Communication Conference in 2006, and through this facilitated the development of the African Science Communication Network and the Southern African Science Communication Network (SASCON) (<http://www.saasta.ac.za/aboutus/background.shtml>). They are members of the International Network on Public Communication of Science and Technology (PCST). South African initiatives such as National Science Week, managed by SAASTA, and Scifest Africa have sought to promote science among the general public, especially the youth.

The focus of SAASTA's initiatives has been influenced by *Africa's Science and Technology Consolidated Plan of Action* (African Union and NEPAD, 2006) which consolidated the science and technology programmes of the African

Union (AU) Commission and NEPAD. The plan is administered by the African Ministerial Council on Science and Technology (AMCOST). One of the aims of the plan is to build “a strong political and civil society constituency for science and technology in Africa” (African Union and NEPAD, 2006:10). But public engagement with science or medicine is not included in the proposed NEPAD indicators for African science, technology and innovation (NEPAD, 2006).

To guide its focus from 2006 to 2010, the plan identified six flagship research and development clusters. These include:

1. Biodiversity, Biotechnology and Indigenous Knowledge;
2. Energy, Water and Desertification;
3. Materials Sciences, Manufacturing, Laser and Post-Harvest Technologies;
4. Information, Communication and Space Science Technologies;
5. Improving Policy Conditions and Building Innovation Mechanisms;
6. Implementation, Funding and Governance.

Yet only one of the flagship areas, biodiversity, biotechnology and indigenous knowledge, relates to medical research, in spite of the enormous contribution medical research can and does make to social and economic development on the continent. The plan is committed to promoting science and technology in the achievement of the Millennium Development Goals (MDGs), and three of the eight goals are health-related (child health, maternal mortality, HIV/AIDS, malaria and other diseases) (African Union and NEPAD, 2006). Clinical research has thus not been sufficiently prioritised in government strategies to promote science and technology.

In the development of new drugs based on **indigenous knowledge of local plants**, South Africa already has a number of initiatives that can be used to increase access to essential generic drugs that are still under patent

protection, and to protect the intellectual property of communities whose knowledge about the use of plants for medicinal purposes is used to create new drugs. The DTI has made a number of modifications in South African law to protect community-based intellectual property (IP), the Department of the Environment and Tourism has gazetted bio-prospecting regulations, and the DST has set up an Indigenous Knowledge Systems unit to manage the development of benefit-sharing agreements between communities and companies wishing to use their IP (Department of Environmental Affairs and Tourism, 2007; Department of Science and Technology, 2004; Patent Amendment Act 2005; Intellectual Property Laws Amendment Bill [Draft] 2009). The Department of Health and the MRC have funded collaborations between indigenous medical practitioners and scientists to test the efficacy of indigenous remedies in laboratories. The **TRAMED (traditional medicine) project** associated with the MRC programme is mainly concerned with testing traditional medicines in clinical settings and has already compiled a plant database (<http://databases.mrc.ac.za/Tramed3>), and the University of the Western Cape Pharmacopoeia monograph project has further data on traditional medicinal plant use (<http://www.sahealthinfo.org/traditionalmeds/monographs.htm>).

One of the examples of benefit-sharing agreements has been the development of an obesity drug from the plant *Hoodia gordonii*, used traditionally by the San to reduce hunger. However, in this case the benefit-sharing agreement refers to a patent on the use of a molecule rather than on the use of the plant itself. It is difficult, although not impossible, to patent the rare and unusual use of a natural plant. Many producers are thus bypassing the *Hoodia* patent and thus earning profits which do not benefit the community concerned (*Business Day* newspaper, 12 July 2006).

As discussed in Chapter 3, much of the intellectual property and research experience generated by clinical trials is located outside of developing countries such as South Africa, and local access to drugs still under patent is limited by their greater cost. Increased African involvement in setting clinical research agendas and improved intellectual property protections

for communities will help to build trust in clinical research, and ensure that benefits important to participant communities accrue from clinical trials. Stabilising research capacity locally requires investment in local opportunities for existing researchers by, for example, locating key research institutions in countries such as South Africa.

Some of these concerns have begun to be addressed by funding clinical trials on locally relevant drugs and local research capacity building, increasing access to early clinical trials data, and developing locally appropriate ethical protocols (Humphreys, 2006; Bosch, 2004; Benatar, 2002). One particularly interesting initiative is the **European and Developing Countries Clinical Trials Partnership (EDCTP)** initiative, which was created in 2003 as a response to the global health crisis caused by the three main poverty-related diseases of HIV/AIDS, malaria and TB. The idea behind the partnership is to help EU member states to integrate and coordinate their own national research and development programmes and form partnerships with their sub-Saharan African counterparts. The EDCTP “aims to accelerate the development of new or improved drugs, vaccines and microbicides against HIV/AIDS, malaria and tuberculosis, with a focus on phase II and III clinical trials in sub-Saharan Africa.” African scientists are well represented on EDCTP’s decision-making governance structures (<http://www.edctp.org/Home.162.0.html>).

In conclusion, there is an agency within SAASTA that is specifically mandated to promote public understanding of science, and a broader African **Plan of Action** (2006–2010) promoting science and technology, but the basic sciences have received more attention than clinical research. There has to date been too little research on how the public responds to science, and specifically to clinical research, and few initiatives to improve this engagement. However, a number of initiatives have been put in place to protect community-held intellectual property over indigenous medical knowledge and to redress the imbalance between local and international scientists in decision-making about clinical trials.

WHAT STILL NEEDS TO BE DONE

Developing a national culture supporting clinical research requires interventions by the clinical research community and by the state. The state can support clinical research through awareness-raising activities, coordinated funding for education of researchers, the activities of research institutions and clinical researchers. Local and regional science and technology-promotion activities need to be integrated and expanded to focus more on clinical research.

The clinical research community and other promoters of clinical research need to engage more with the public about the aims, processes and results of research to improve public trust and participation in research, but also to improve their own understanding of community needs, to improve community access to the benefits accruing from research and to inform research ethics models. It is critically important for the science fraternity to start to engage in open debates with other stakeholders about the nature and role of science, and how to use science and other sources of knowledge to address issues of public concern. In an environment where science is not necessarily trusted on its own terms, rumours are a vehicle through which the public can debate feelings of ambivalence about “the advantages (free treatment) and disadvantages (giving blood) of participation in research, and issues of inequality and the fair distribution of benefits.” In medical research in Africa the issue of inequality and fairness has to be something researchers negotiate with research participants rather than simply impose on them (Geissler and Pool, 2006). Dialogues between scientists and the public about these misunderstandings thus have to happen “if medical research in resource-poor settings is to continue to be sustainable and politically legitimate” (Fairhead *et al.*, 2006b).

In the UK a new **Sciencewise** funding scheme funds public engagement with science in the context of developing public policy on new technologies. The project uses public engagement to achieve three main aims (<http://www.sciencewise-erc.org.uk/cms>):

1. *to inform and strengthen policy recommendations, provide legitimacy to decisions and lead ultimately to better legislation that benefits all society;*

2. *to provide opportunity for exchanges between scientists and the public, not only to provide and debate scientific information but also information about the social context and moral environment in which science policy decisions must work;*
3. *to develop public trust in the use of science and new technologies in driving the country's development, and to make their views on acceptability of new technologies heard.*

One of the associated initiatives, the UK Clinical Research Collaboration (UKCRC), is "a partnership of organisations working to establish the UK as a world leader in clinical research, by harnessing the power of the NHS." Part of this programme includes setting up Patient and Public Involvement programmes and Public Awareness groups (UK Clinical Research Collaboration, 2008-2011). A number of projects were initially developed and delivered, including the recruitment of patient/public members to key UKCRC Boards and Advisory Groups; materials aimed at raising public awareness and understanding of clinical research; and People in Research, a web-based resource which helps patients and members of the public make contact with organisations that have opportunities for patient and public involvement (<http://www.peopleinresearch.org>). The Social Issues Research Centre (with the Royal Society) and the Royal Institution of Great Britain have published guidelines on science and health communication (<http://www.sirc.org>). The Patient and Public Involvement Strategic Plan 2008 – 2011 seeks to increase patient and public involvement in clinical research at a strategic level, improve public understanding of and confidence in clinical research, and develop the sustainability of patient and public involvement in the UK (<http://www.ukcrc.org>). A recent survey of public attitudes to science in the UK follows similar surveys in 2000 and 2005 (<http://www.sirc.org>).

A number of other projects have emerged internationally from increasing interest in improving the engagement between science and the public. Not all of these projects are government initiatives. **Observa – Science in Society** (<http://www.observa.it>)- **is, for example, a 'non-profit cultural association' of**

academics in a number of European institutions, affiliated with no private or public organisations, which aims at “promoting the study and the discussion of the interaction between science and society, stimulating dialogue among researchers, policy-makers and citizens.” *Observe* focuses on three main areas: Science Communication; Research and Innovation Policy; and Science, Citizens and Technology (<http://www.observa.it>). In the US, the Clinical Research Forum was established in 1996 and refocused in 2005 to “provide leadership to the national clinical and translational research enterprise and to promote understanding and support for clinical research and its impact on health and health care” (<http://www.clinicalresearchforum.org>). It promotes public understanding and participation in clinical research. The National Science Board in the US has given annual public service awards since 1996 to key people (not just scientists) who have promoted public understanding of science and science literacy in various science fields, including medicine, and engineering (National Science Foundation, <http://www.nsf.gov>; http://www.nsf.gov/nsb/awards/public_recipients.jsp). The Royal Society in the UK offers the Kohn Award for excellence in engaging the public with science, and the Michael Faraday award for science communication (<http://www.royalsociety.org>).

Other kinds of initiatives include the Edinburgh International Science Festival and the London Summer Science Exhibition, the Australian Science Festival (from 1988) and the World Science Festival in New York. Many countries celebrate science weeks and research weeks – Brazil has a National Week of Science and Technology in which scientists speak to schoolchildren (<http://www.rnp.br/en/news>); television is also a key part of the Brazilian public strategy to develop interest and knowledge about science (Barata and Jorge, 2008). The Philippines started an Annual National Health Research System (PNHRS) Week in 2007, based on a partnership between the Department of Science and Technology and the Department of Health to which the Commission on Higher Education (CHED) and University of the Philippines - National Institutes of Health (UP-NIH) have been added. The week has a theme (the theme for 2008 was strengthening networking and convergence within the PNHRS), and includes training sessions on research article writing, writing policy briefs and

proposal development in accessing research funds from the Department of Science and Technology (DST), CHED and the University of the Philippines – National Institutes of Health (UP-NIH). Conferences associated with the event include scientific sessions focusing on priority areas identified in the ASEAN Plan of Action on Science and Technology (APAST) such as functional food, open source technology, alternative energy, and disaster mitigation. There will be separate sessions on capacity building and intellectual property to cover topics on human resource development, intellectual property rights, technology transfer mechanisms, and strategies adopted by ASEAN member countries to develop science and technology capability (Asmolo, 2008).

Academic interest in public understanding of science has also increased. The London School of Economics (<http://www.lse.ac.uk>) has a research programme called STEPS: Science, Technology and the Public Sphere. Various university chairs, courses and departments specialising in this area have been established. A Chair for the Public Understanding of Science at Oxford University in the UK was founded in 1995 (Charles Simonyi Professorship in the Public Understanding of Science, Oxford University, <http://www.admin.ox.ac.uk/fp/wd9-018.shtml>). The aim of the professorship is to communicate science to the public outside the University, including non-specialists and also those in opinion-forming positions without, in doing so, 'dumbing-down' the science. The Chair is expected to play a role in developing the science outreach activities of the University and its museums (<http://www.admin.ox.ac.uk>). In Australia, the Centre for the Public Awareness of Science (CPAS) (<http://en.wikipedia.org/wiki/CPAS>) was established at the Australian National University (ANU) in 1996. Foreshadowing the conclusion reached by the British House of Lords more than ten years later, CPAS adopted the philosophy of 'Public Awareness'. Its thrust was not directed solely at increasing public understanding of science. Rather, it was concerned with increasing public awareness of science, fostering in the community a 'need to know', and encouraging the community to take possession of science and orchestrate its own learning. CPAS offers graduate education in science communication, including master's and PhD programmes, which have proved very popular (<http://www.en.wikipedia.org>). It has also funded various initiatives for

promoting science in South Africa (see also http://en.wikipedia.org/wiki/Science_communication#cite_note-15).

The UK-based James Lind Alliance is an initiative that aims to include the public in identifying and confronting uncertainties about the effects of treatments considered important by both patients and clinicians (<http://www.lindalliance.org>). Funded by the British Medical Research Council and the UK Department of Health, the Alliance promotes two principles: first, that addressing uncertainties about the effects of treatments should become accepted as a much more routine part of clinical practice; and second, that patients and clinicians should work together to agree which, among those uncertainties, matter most and thus deserve priority attention. Meetings between the general public and clinicians are organised to prioritise research areas and a database, the **Database of Uncertainties about the Effects of Treatments (DUETs)**, has been established. DUETS aims to identify and publish uncertainties reflected in patients' and clinicians' questions about the effects of treatments which cannot be answered by referring to up-to-date systematic reviews of existing research evidence. DUETS is being used to inform priorities for new research, in particular those identified through working partnerships of patients and clinicians.

In the developing world, the basic concept of **democratic engagement on difficult issues** remains relevant, although programmes promoting public engagement with science would need to focus on development policy goals such as science education and health. These public debates need to be carefully prepared, but should also aim at starting productive mutually respectful dialogue on solving a common problem, rather than being staged to 'produce' a positive view of science. Debate could be fostered both within clinical trial contexts and outside of them, as a way of understanding public views and addressing public concerns about clinical research. The proposed National Health Research week could integrate well with existing projects such as National Science Week and Scifest Africa, and provide a focus for open discussions about the role of research and the relationship between Western science and indigenous medicine. Churches, activist

groups, traditional healers and community leaders could play a role in such discussions. A **National Clinical Research Society** or Network could, together with ASSAf, promote research and projects to improve public engagement with clinical research as part of a broader agenda promoting excellence and relevance in clinical research.

The roles of **health and science journalists** and the media in general also need to be addressed in relation to the theme of this chapter. Clinical researchers are often antagonistic to what they perceive as excessive sensationalism and inaccurate reporting; this does not help them, as the antagonism is often exacerbated by off-handedness and evasion. Suffice it to say that no approach to the public understanding of clinical science will succeed if it does not take into account the importance of the media.

More attention also needs to be paid to developing a **bottom-up approach to ethics in clinical trials**: understanding community fears and needs, encouraging more community involvement in assessing the ethical conduct of medical research and negotiating what benefits will accrue to trial participants (Geissler and Pool, 2006; Buchanan *et al.*, 2008). Researchers need to try and understand how the public perceives them and their research institutions, not just as producers of important knowledge, but as players within the local socio-economic context (Fairhead *et al.*, 2006b). As we have pointed out above, simply providing scientific facts and dismissing public views as ignorance and rumour is not productive in addressing misperceptions. Researchers need to justify their research to participants in terms of concrete outcomes. Forums for identifying mutual interests and concerns among researchers, activists and participants, based on principles of reciprocity and transparency, can be used to identify early public concerns about trial participation (Singh and Mills, 2005). Trying to understand rumours about blood and organ trafficking, deliberate spreading of disease, and surreptitious birth control could “enrich medical research ethics debates and improve relations between medical researchers and study communities” (Geissler and Pool, 2006). Other mechanisms to improve researcher-community relationships in trials could include the appointment of community liaison officers, the use of prior fact-

finding missions on operational issues, confidence-building measures (such as the inclusion of activist groups in community advisory boards), engaging the media, and education (e.g. on therapeutic misconception, compensation for study-related injuries, and post-trial benefits) (Singh and Mills, 2005). This can improve mutual understanding about what clinical trial participants and researchers believe they are exchanging with each other in the trial context, and reduce misunderstandings about their respective roles. Where there is direct benefit in terms of drug access, better feedback can improve adherence or take-up of new therapies. Ultimately, making a more direct link between research and fair benefit to participants (from their own viewpoint) will be the best way of fostering trust in scientific research and encouraging participation in future trials.

Building a broader public culture supportive of clinical research requires that the benefits, biases and challenges of the clinical trials industry are debated and addressed. South Africa already has a number of initiatives to address such challenges. These initiatives should be more widely publicised and better integrated.

FINDINGS

1. There has been too little research on the public understanding of science or on public perceptions of clinical trials in South Africa.
2. There is a legacy of distrust and ignorance in the relationship between research participants and clinical researchers because of the history of South Africa. Mutually beneficial engagement between the public and clinical researchers has not been extensive enough in the past.
3. South Africa is an attractive location for clinical trials, *inter alia* because it has a good clinical infrastructure, low levels of litigation, a credible regulatory environment, and a full spectrum of health problems. Recruitment for clinical trials has been relatively easy in South Africa due to a large treatment-naïve urban population, who experience high unemployment and difficulty accessing expensive drugs.

RECOMMENDATIONS

1. Raise the profile of clinical research on the continent: for example, in the African Science Communication Network and the Southern African Science Communication Network (SASCON), and include clinical research as a further flagship research and development cluster for the 2011–2015 ***African Science and Technology Plan of Action***.
2. Raise the profile of clinical research within South Africa: for example, broaden National Science Week to incorporate a National Health Research week; establish an ASSAf award for Promoting Public Engagement with Clinical Science.
3. Improve public engagement with science: for example, fund qualitative and quantitative research about the public understanding of science in southern Africa within universities and research institutions; motivate for an NRF Research Chair in Public engagement with Science and ensure there are clinical candidates; include public engagement with science in the NEPAD Indicators for African science, technology and innovation.
4. Review the new curriculum statements in schools: refer specifically to therapeutic/clinical concepts based on an historical (longitudinal) approach in order to make useful connections between chemistry, human physiology (e.g. endocrinology as an internal 'drug-administering system'), mathematics literacy, ethics and economics.
5. Ensure a more democratic engagement between the public and researchers, and help to ensure that they share a common understanding about the operation and purpose of clinical research, for example by:
 - a. **developing locally appropriate public communication guidelines and ethical protocols for researchers;**
 - b. **engaging with public views about clinical research, including geopolitical issues as part of research preparation activities;**

c. promoting rights access and education for trial participants.

6. Promote health and science journalism and effective interfaces between the media and the clinical research community.

REFERENCES FOR CHAPTER 4

African Union and NEPAD. *Africa's Science and Technology Plan of Action*, pp. 8, 10. Available at: http://www.nepadst.org/doclibrary/pdfs/doc27_082005.pdf.

Asmolo, R. M. 2008. 2nd PNHRs Week themed Converge@ PNHRs! Press release, Philippine Council for Health Research and Development, Thursday, 24 July 2008. Available at: http://www.pchrd.dost.gov.ph/index.php?option=com_content&task=view&id=281&Itemid=1.

Baldwin-Ragaven, L., De Gruchy, J. and London, L. 1999. *An ambulance of the wrong colour: Health professionals, human rights and ethics in South Africa*. Cape Town: UCT Press.

Barata, G. and Jorge, W. 2008. *Digital TV system in Brazil: New perspective for science communication*, *Observe: Science in Society*. Available at: http://www.observa.it/public/docs/Barata_Jorge_TVContributoxObserve15022008.pdf.

Barsdorf, N. W. and Wassenaar, D. R. 2005. Racial differences in public perceptions of voluntariness of medical research participants in South Africa. *Social Science and Medicine*. 60(5): 1087-1098.

Benatar, S. R. 2002. Reflections and recommendations on research ethics in developing countries. *Social Science and Medicine*. 54: 1131-1141.

Blankley W. and Arnold, R. 2001. Public understanding of science in South Africa – Aiming for better intervention strategies. *South African Journal of Science*, 97(3-4): 65-69.

Bosch, X. 2004. Clinical trials partnership seeks to boost research in developing countries. *Journal of the American Medical Association*. 292(11): 1290; see also Benatar (above).

Buchanan, D., Sifunda, S., Naidoo, N., James, S. and Reddy, P. 2008. Assuring adequate protections in international health research: A principled justification and practical recommendations for the role of community oversight. *Public Health Ethics*. 1: 246-257.

Buckley, B. 2008. The need for wider public understanding of health care research. *Primary Health Care Research & Development*. 9: 3-6.

Bunting, I. 2002 and Cloete et al. 2002. Cited in J. Mouton, N. Boshoff and T. Bailey, 2002. *Promoting South African Science and Technology capacities for the 21st century: From policy to reality*. Background document, Proceedings of the Academy of Science of South Africa (ASSAf) Consultative Forum, 13-14 September 2002, pp. 44-45. Available at: <http://blues.sabinet.co.za/images/ejour/assaf/background.doc>.

Business Day newspaper. 2006. Struggle over Hoodia patent continues. 12 July 2006, p. 6.

Campion-Vincent, V. 2002. Organ theft narratives as medical and social critique. *Journal of Folklore Research*. 39: 33-50.

Chandler, A. D. 2005. *Shaping the Industrial Century: The Remarkable Story of the Evolution of the Modern Chemical and Pharmaceutical Industries*. Harvard: Harvard University Press.

Clinical Research Forum. Available at: <http://www.clinicalresearchforum.org/initiatives.cfm>.

Cohen. 1997; Smith and Nicodemus. 1999; and Schoofs. 2001. Cited in Barsdorf, N.W. and Wassenaar, D. R. 2005. Racial differences in public perceptions of voluntariness of medical research participants in South Africa. *Social Science and Medicine*. 60(5): 1087-1098.

Comaroff, J. and Comaroff, J. L. 1999. Occult economies and the violence of abstraction: Notes from the South African postcolony. *American Ethnologist*. 26: 279-303.

Department of Environmental Affairs and Tourism (South Africa). 2007. Draft regulations on bio-prospecting, access and benefit sharing. *Government Gazette*, 16 March 2007, No. 29711 19.

Department of Science and Technology (South Africa). 2004. *Indigenous Knowledge Systems Policy*.

Digby, A. 2006. *Diversity and division in medicine: Health care in South Africa from the 1800s*. Oxford: Peter Lang. p. 368.

Edigheji, O. 2008. Paper presented at the Conference on the Potentials for and Challenges of Constructing a Democratic Developmental State in South Africa, Human Sciences Research Council, 4-6 June, 2008, Cradle of Humankind, Gauteng.

Editorial, 'The Reluctance of Black People to Participate in Clinical Medical Research'. *The Journal of Blacks in Higher Education*. No. 17. (Autumn, 1997), pp. 33-34.

European and Developing Countries Clinical Trials Partnership (EDCTP). Available at: <http://www.edctp.org/Home.162.0.html>.

Fairchild, A. L. and Bayer, R. 1999; and Bull. 2003. Cited in N.W. Barsdorf and D. R. Wassenaar, Racial differences in public perceptions of voluntariness of medical research participants in South Africa, *Social Science and Medicine*. 60(5).

Fairhead, J., Leach, M. and Small, M. 2006a. Where techno-science meets poverty: Medical research and the economy of blood in The Gambia. *Social Medicine*. 63: 1109-1120.

Fairhead, J., Leach, M. and Small, M. 2006b. Public engagement with science? Local understandings of a vaccine trial in The Gambia. *Journal of Biosocial Science*, 38: 103-116.

Funke, N., Nortje, K., Strydom, W., Van Wyk, E., Macmillan, P., Rascher, J. and Weaver, A. 2008. Understanding the dynamics of the uptake of Research and Development results in a developing South African context. Pretoria: CSIR report on a workshop. p. 8, 77.

Geissler, P. W. 2005. Kachinja are coming! Encounters around a medical research project in a Kenyan village. *Africa*. 75: 173-202.

Geissler, P. W. and Pool, R. 2006. Editorial: Popular concerns about medical research projects in sub-Saharan Africa – A critical voice in debates about medical research ethics. *Tropical Medicine and International Health*. 11: 7.

Humphreys, G. 2006. Clinical trials Initiative: Patients or patents? *Bulletin of the World Health Organisation*. 84(7): 513.

Lecouturier, J., Rodgers, Ford, G. A., Rapley, T., Stobbart, L., Louw, S. J. and Murtagh, M. J. 2008. Clinical research without consent in adults in the emergency setting: A review of patient and public views. *BMC Medical Ethics*. 9: 9.

Legassick, M. and C. Rassool. 2000. *Skeletons in the Cupboard: South African Museums and the Trade in Human Remains, 1907-1917*. Cape Town: South African Museum.

Indegger, G., Quayle, M. and Ndlovu, M. 2007. Local knowledge and experiences of vaccination: Implications for HIV-preventive vaccine trials in South Africa. *Health Education & Behavior*. 34(1): 108-123.

London School of Economics and Political Science. Available at: <http://www.lse.ac.uk/collections/socialPsychology/research/scienceTechnologyAndPublic.htm>.

Lurie, P. and Wolfe, S. M. 1997. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine*. 337(12): 853-856.

Mayosi, B. 2008. Department of Medicine, Groote Schuur Hospital and University of Cape Town. Personal communication.

Molyneux, C. S., Mutemi, W. and Marsh, K. 2005. Trust and informed consent: Insights from community members on the Kenyan Coast. *Social Science & Medicine*. 61: 1463-1473.

Molyneux, C. S., Peshua, N. and Marsh, K. 2004. Understanding of informed consent in a low-income setting: Three case studies from the Kenyan coast. *Social Science & Medicine*. 59: 2547-2559.

Mouton, J., Boshoff, N. and Bailey, T. 2002. Promoting South African Science and Technology capacities for the 21st century: From policy to reality. Background document, Proceedings of the Academy of Science of South Africa (ASSAf) Consultative Forum, 13-14 September 2002. pp. 44-45. Available at: <http://blues.sabinet.co.za/images/ejour/assaf/background.doc>.

National Week of Science and Technology in Brazil. Available at: <http://www.rnp.br/en/news/2004/not-040922.html>.

Nchito, M. F., Geissler, P. W., Mubila, L., Friis, H. and Olsen, A. 2003. The effect of iron and multi-micronutrient supplementation on *Ascaris lumbricoides* reinfection among Zambian schoolchildren – A two-by-two factorial study. *Transactions of the Royal Society for Tropical Medicine and Hygiene*. 98: 218–227.

NEPAD. 2006. African Science, Technology and Innovation Indicators: Towards African Indicator Manuals: A discussion document. Available at: http://www.nepadst.org/doclibrary/pdfs/iastii_jun2006.pdf.

Niehaus, I. 1993. Coins for blood and blood for coins: Towards a genealogy of sacrifice in the Transvaal Lowveld. Paper read at a meeting of the Society for South African Anthropology, Johannesburg.

Observa: Science in Society. Available at: <http://www.observa.it/comitatosciencecoobserva.aspx?LAN=ENG>.

Patent Amendment Act, Act No. 20 of 2005.

People in Research. Available at: <http://www.peopleinresearch.org>.

- People, Science and Policy Ltd. (UK Department for Innovation, Universities and Skills). 2008. Public attitudes to science. A survey. Available at: <http://www.rcuk.ac.uk/cmsweb/downloads/rcuk/scisoc/pas08.pdf>.
- PlusNews, 7 February 2007. Available at: <http://www.plusnews.org/Report.aspx?ReportId=70022>.
- Pool, R. and Geissler, P. W. 2005. Medical Anthropology. London: The Open University Press.
- Scheper-Hughes, N. 1996. Theft of life: Organ-stealing rumors. *Anthropology Today*. 12: 3-10.
- Scholtz, H. and Pretorius, S. 2005. Discovering South Africa. *Applied clinical Trials online*, 1 June 2005.
- Sciencewise. Available at: <http://www.sciencewise-erc.org.uk/cms>.
- Shepherd, N. 2007. Archaeology dreaming. *Journal of Social Archaeology*. 7(1): 3-28.
- Shisana, O., Rehle, T., Simbayi, L., Parker, W., Zuma, K., Bhana, A., Connolly, C., Jooste, S., Pillay, V. et al. 2005. South African national HIV prevalence, HIV incidence, behaviour and communication survey, 2005. Cape Town: Human Sciences Research Council. p. xxiv.
- Singh, J. A. and Mills, E. J. 2005. Cited in P. W. Geissler and R. Pool. 2006. Editorial: Popular concerns about medical research projects in sub-Saharan Africa – A critical voice in debates about medical research ethics. *Tropical Medicine and International Health*. 11(7): 975.
- Singh, J. A. and Mills, E. J. 2005. The abandoned trials of pre-exposure prophylaxis for HIV: What went wrong? *PLoS Medicine* 2: e234.
- Smith, C. and Nicodemus, A. 1999. More human guinea pigs for Virodene. *The Mail & Guardian newspaper*, 19 March 1999. Available at: <http://www.q.co.za/news/1999/9903/990319-virodene.htm>.
- Smith, R. 2000. UK is losing market share in pharmaceutical research. *British Medical Journal*. 321: 1041.
- Social Issues Research Centre with the Royal Society and the Royal Institution of Great Britain. Guidelines on Science and Health Communication. Available at: http://www.sirc.org/publik/revised_guidelines.shtml.
- South African Health Information. Available at: <http://www.sahealthinfo.org/traditionalmeds/monographs.htm>.
- South African Medical Research Council database. Available at: <http://databases.mrc.ac.za/Tamed3>.
- Swartz, L. and Kagee, A. 2006. Community participation in AIDS vaccine trials: Empowerment or science? *Social Science & Medicine*. 63(5): 1143-1146.
- Tucker, T. J. and Makgoba, M. W. 2008. Public-private partnerships and scientific imperialism. *Science*. 320: 1016-1017.
- UK Clinical Research Collaboration, Patient and Public Involvement Strategic Plan 2008– 2011 Available at: <http://www.ukcrc.org/pdf/UKCRC%20PPI%20Strategic%20Plan%2&%2Report%2April08.pdf>, p.4.
- Williams, B., Entwistle, V., Haddow, G. and Wells, M. 2008. Promoting research participation: Why not advertise altruism? *Social Science & Medicine*. 66: 1451-1456.

CHAPTER 5:

ENHANCING ETHICAL OVERSIGHT OF CLINICAL RESEARCH
TO PROTECT INDIVIDUALS AND COMMUNITIES

In this chapter, we engage with the following questions:

1. What are the current mechanisms for ethical oversight for clinical research in South Africa?
2. How well are these mechanisms functioning?
3. How do ethical oversight mechanisms for clinical research function elsewhere?
4. How can we improve ethical oversight for clinical research in South Africa?
5. How can ethical publication practices be ensured?

INTRODUCTION

The fundamental role of clinical research in the provision of high-quality care is well documented (Moerman *et al.*, 2007). Biomedical research is yielding new diagnostic and therapeutic methods at an accelerating rate (Patenaude *et al.*, 2007) and this provides health care professionals with information on optimal strategies for the prevention, diagnosis and treatment of health conditions (Moerman *et al.*, 2007). About 100 000 clinical trials are carried out around the world each year, with 10% being done in developing countries (Watson, 2007). In 2000, South Africa was reported to be handling 0.6% of global trials, although it had the capacity to conduct 2.5% of the world's clinical research contracts (Baird and Niekerk, 2004). The **global clinical trials business** was worth an estimated US\$50 billion in 2008, with a rate of growth of 10% (Global Clinical Trials Business Report & Analysis, 2008-2018). In South Africa, clinical research was worth approximately US\$1.5 billion in 2006 (<http://www.crc-sa.com>) and there was a 40% growth between 1997 and 1998 in the clinical research industry, mainly as a result of the ability of researchers being able consistently to meet patient recruitment timelines and targets (Dhai, 2005). There has recently been a decline in industry-related clinical trials at

academic institutions, however, as evidenced by a 16% reduction in clinical trials applications to the University of Witwatersrand's Human Research Ethics Committee (HREC) between 2003 and 2007 (Cleaton-Jones and Vorster, 2008). A similar trend was reported at the Biomedical Research Ethics Committee of the University of KwaZulu-Natal, where there was a 36% decline in industry-related applications between 2000 and 2004 (Dhai, 2005). This decline in industry-related clinical studies at academic institutions has been confirmed by the Medicines Control Council of South Africa (MCC). The impact of clinical research on the health and economy of any country emphasises the need to keep the research enterprise afloat. Various initiatives such as the European roadmap for initiative research have been recommended as measures to identify and train best researchers in universities, laboratories, industry and health care settings (Groves, 2008).

Identifying barriers to the successful conduct of research plays an important role in promoting and safeguarding the clinical research enterprise. Addressing challenges that present at different levels in research in South Africa would assist in driving clinical research to flourish. This must be done in a manner that also respects human rights and dignity. **Ethical principles and values**, such as respect for persons, beneficence, non-maleficence, justice and respect for human dignity must underscore all health research activities. Obtaining **informed consent** from prospective research participants is a vital requirement if research is to be conducted ethically. Barriers to the informed consent process in South Africa are language, culture and vulnerabilities associated with poverty and massive socio-economic disparities. Benefits to participants and communities who are involved in research should outweigh potential harms and risks. Moreover, benefits and risks of the research should be distributed equitably in society, both locally and globally. If research is to be carried out in South Africa, research participants and communities should have access to interventions that are proven to be efficacious. **Standards of care** should be equal for all during research, thereby demonstrating equal respect for research participants' dignity. In addition, research participants should not be expected to bear the costs of trial participation, i.e. management of trial-related injuries should be the researcher's and not the participant's responsibility. A

requirement of justice is that the trial should leave the participant better off, or at least no worse off.

In this chapter, we look at (i) the law governing the conduct of research, (ii) ethics governance, i.e. RECs: their composition, functions, workloads and funding, and (iii) existing instruments and processes for the facilitation and promotion of research. We make recommendations to facilitate the promotion of ethical clinical trials research.

THE SOUTH AFRICAN LAW GOVERNING CLINICAL RESEARCH

Regulations governing clinical research serve the purpose of providing ethical and scientific quality standards for designing, conducting, recording and reporting trials that involve participation of human participants (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice [ICH-GCP]). Failure of the research enterprise might be a reflection of the relative failure of national regulations to have a downstream effect on the practices of research staff (Rab *et al.*, 2008). In South Africa, Chapter 9 of the **National Health Act, Act 61 of 2003**, makes the conduct of *ethical* health research a legal requirement. Health research is defined in the National Health Act as any research that contributes to knowledge of:

1. The biological, clinical, psychological or social processes in human beings;
2. Improved methods for the provision of health services;
3. Human pathology;
4. The causes of disease;
5. The effects of the environment on the human body;

6. The development or new applications of pharmaceuticals, medicines and related substances;
7. The development of new applications of health technology.

The rapid proliferation of clinical trials, where clinical trials are defined as a systemic study involving human subjects that aims to answer specific questions about the safety or efficacy of a medicine or method of treatment (section 72(7) of the National Health Act), and the increasingly complex regulations governing research (Chaddah, 2008) have had a negative impact on the continued growth of research. While some concerns have been raised that the protection of research participants is often assumed to be inadequate in the formulation of policy or legislation, other concerns exist that protection programmes result in **overregulation**, increasing the time and expense devoted to activities of marginal utility in protecting human research participants (Fost and Levine, 2007: 2196).

South Africa has a well-established regulatory process based on guidelines for clinical studies (Scholtz and Pretorius, 2005). Section 12 of the **Bill of Rights of the Constitution of South Africa, Act 108 of 1996**, affirms that no one will be involved in medical experimentation without providing informed consent. The National Health Act stipulates the basic ethical requirements in the conduct of research. The principles emphasised in the Act include confidentiality (section 16) when using medical records for research purposes, respect for persons, and autonomy by allowing self-determination in the requirement for written informed consent form (section 71). These principles are also found elsewhere in the regulations governing research in South Africa, including the **South African Good Clinical Practice guidelines**, 2nd Edition 2006, and the Department of Health's **Research Ethics Guidelines**, 2004. Enshrined in Chapter 9 of the National Health Act is section 69 which provides for the establishment of a **National Health Research Committee**. This committee is mandated in terms of the Act to identify research priorities of the nation (section 70). Realisation of distributive justice is enhanced through this provision as this section serves to eliminate research that is biased towards an elite group while disregarding

the needs of the poorer communities. Inadequate protection of research participants could have deleterious effects on research, as participants might be less willing to engage in research (Campbell, 2004). Section 72 of the National Health Act provides for the establishment of a National Health Research Ethics Council (NHREC). This Council, which was established in October 2006, has been directed by the Act to establish **Research Ethics Committees (RECs)** accredited with it and to register and accredit existing RECs. Flawed implementation of regulations by local RECs or in the governing regulations themselves where investigators perceive problems could stifle research activities (Whitney *et al.*, 2008: 71). The former is likely to be minimised through the **accreditation process** when it is implemented, however, as the NHREC will monitor and investigate the policy standards and standard operating procedures, training and capacity building, appeals and subcommittees of local RECs (Article 3.2, Ethics Guidelines, 2004).

The **statutory functions of the NHREC** include:

- a) **Determining guidelines for the functioning of health research ethics committees;**
- b) **Registering and auditing health research ethics committees;**
- c) **Setting norms and standards for conducting research on humans and animals, including norms and standards for conducting clinical trials;**
- d) **Adjudicating complaints about the functioning of health research ethics committees;**
- e) **Hearing any complaint by a researcher who believes he or she has been discriminated against by a health research ethics committee;**
- f) **Referring to the relevant statutory health professional council matters involving the violation or potential violation of an ethical or professional rule by a health care provider;**
- g) **Instituting such disciplinary action as may be prescribed against any person found to be in contravention of any norms, standards or guidelines set for the conducting of research in terms of the National Health Act;**

h) Advising the national and provincial departments on any ethical issues concerning research.

The NHREC therefore has obligations to both researchers and research participants to ensure the creation of an enabling environment for the conduct of ethical clinical research. It is imperative that the NHREC is supported by the national Department of Health in implementing its mandate. It is also imperative that implementation is carried out efficiently and without delay and that members of this very important Council have the necessary competence to allow for the optimal functioning of this body. In addition, both researchers and health research ethics committees need to be aware of the NHREC, its mandate and any pertinent ethics guideline documents emanating from it to allow for informed decisions on the ethical aspect of studies. Functional knowledge and understanding of ethics in research on the part of health research ethics committee members would also serve to facilitate the research process rather than stifle it as is currently the common perception. Stifling of research due to a lack of awareness of national and international guidelines by REC members, as reported by Ikungura *et al.* (2007) for Tanzania (>50%), could be minimised through the accreditation process.

In terms of section 73 of the National Health Act, every institution, health agency and health establishment at which health research is conducted, must establish or have access to a **health research ethics committee**, which is registered with the National Health Research Ethics Council. The provision further outlines the functions of the RECs, including review of research proposals. Within the South African regulatory framework, limitations are placed on RECs with regard to the type of proposals that they are allowed to review based on their accreditation level. Article 3.3.2 of the Ethics Guidelines (2004) articulates that RECs would be accredited as either **Level 1 or Level 2**, depending on the capacity of the committee. Level 1 committees would assess straightforward research designs that involve minimal risk to human participants or low budget research (less than R250 000). Level 2 committees would review all types of health research proposals. This division of committee functioning could help to expedite review of minimal-risk research. It has been

stated, however, that the danger with this division is that it could encourage the diversion of resources from areas of greater need to minimal or no-risk research (Gunsalus, 2006; Boronstein, 2007) because of the perception that there would be less stringent review. Other concerns include the fact that the accreditation systems could reduce the number of operating RECs and discriminate against historically disadvantaged institutions (Moodley and Myer, 2007).

ETHICS GOVERNANCE: REC COMPOSITION, FUNCTIONS, WORKLOADS AND FUNDING

Composition of RECs

The quality and efficiency of protocol review by an REC is fundamentally a function of its **aggregate expertise**. It is possible that difficulties could emerge if an REC examines a research protocol where it lacks expertise within its membership in the respective fields of inquiry (Boronstein, 2007). Many countries have developed formal regulations governing the composition of ethics committees to ensure that specific expertise is present, such as biomedical and biometrical expertise, ethical and legal competence and expertise on issues regarding patients (Moerman *et al.*, 2007). The European Union (EU) directive (Article 2.1k) states that ethics committees should be independent bodies in each member state, consisting of both health care professionals and non-medical members (Hedgecoe, 2006). The same is provided in a regulation of the FDA which articulates that “the IRB shall be sufficiently qualified through experience and expertise of its members, and diversity of its members” (Moodley and Myer, 2007).

The South African National Ethics Guidelines of 2004, in section 4, affirm that the primary role of RECs is to protect the rights and welfare of research participants.

The primary role of each committee member is to decide, independently, whether in his or her opinion, the conduct of the proposed research will protect the participants. Section 4 goes on to place an obligation on institutions where health research is undertaken to ensure that there are adequate resources to

establish and maintain a REC in accordance with national and international norms and standards. A further obligation placed on institutions is that they accept legal responsibility for the decisions and advice received from the REC, and that they also indemnify the REC members.

A REC should thus consist of members who collectively have the qualifications and experience to review and evaluate the science, health aspects and ethics of proposed human-subject research, and should be independent, multidisciplinary, competent and pluralistic. The REC must be representative of the communities it serves and, increasingly, reflect the demographic profile of the population of South Africa, and must include:

1. Members of both genders, although not more than 70% should be either male or female;
2. At least nine members, with 60% constituting a quorum;
3. At least two lay persons who have no affiliation to the institution, are not currently involved in medical, scientific or legal work and are preferably from the community in which the research is taking place;
4. At least one member with knowledge of, and current experience in, areas of research that are likely to be regularly considered by the ethics committee;
5. At least one member with knowledge of, and current experience in, the professional care, counselling or treatment of people. Such a member might be, for example, a medical practitioner, psychologist, social worker or nurse;
6. At least one member who has professional training in both qualitative and quantitative research methodologies;
7. At least one member who is legally trained.

Most of the RECs in the country that are affiliated to health sciences institutions have organised, or are currently in the process of organising, their membership and standard operating procedures to be in line with these guidelines and the National Health Act. At most institutions, however, support for, and commitment to, these processes lag far behind. Furthermore, REC workloads are also increased as a result of the breadth of the definition of health research, resulting in an ever-larger number of studies being submitted for ethics review and approval. Local REC members undertake their work in nearly all cases as volunteers, over and above their daily professional activities (Cleaton-Jones, 2007). REC members are usually faculty staff who struggle to combine their busy service commitments with REC activities.

The **size of RECs** in Africa ranges from nine to 31 members, with the majority of members being clinicians and physicians (Kass *et al.*, 2007). RECs in South Africa typically comprise seven to 29 individuals, with a median of 16 members (Moodley and Myer, 2007) of which 46–82% are men and 18–54% are women. None of the RECs in Africa require gender balance, although all consciously include women (Kass *et al.*, 2007), save for South Africa which has regulations stating that not more than 70% should be of the same sex (Article 4.1, Ethics Guidelines, 2004). The majority of REC members in South Africa are health scientists/clinicians who make up 61% of membership, compared with 49% in the US (Moodley and Myer, 2007), with ethicists being under-represented (Milford *et al.*, 2006). There is usually a provision for at least 25% lay member representation to prevent intimidation of lay members during REC deliberations. While regulations require that lay members should be part of the community being researched, Moodley and Myer (2007) showed that this is not always the case. Most RECs have at least one full-time administrative staff member.

The **skewed composition** of RECs results in a lack of expertise on RECs in many African countries, which impedes research (Ikungura *et al.*, 2007). In South Africa, lack of diversity of expertise within RECs is attributable to the nature of the faculty community where most of these committees are housed (Moodley and Myer, 2007). It is questionable whether RECs have adequate capacity for effective assessment of 'non-biomedical' protocols (Boronstein, 2007). Lack

of diversity on the RECs, which are typically made up of researchers and physicians, leads to bias towards quantitative research (Green *et al.*, 2006:215; Milford *et al.*, 2006), and a tendency to engage mainly with technical issues that fall outside the expertise of non-scientists (Schuppli and Fraser, 2007). Lack of expertise, accountability and open dialogue is also prominent in self-appointed private commercial and non-commercial RECs (Milford *et al.*, 2006). Some private RECs have full-time members and review protocols more frequently (Moodley and Myer, 2007).

How members are appointed onto the RECs determines the expertise that exists in these committees. The Portuguese government nominates all 34 members of a central ethics committee in Portugal – the Ethics Committee for Clinical Investigation (CEIC) (Hedgecoe, 2006). The appointment of members of both the central ethics committee and local ethics committees in Sweden is by the Swedish Government (Hedgecoe, 2006). In Canada, university administrators, such as the vice-president of research, are formally responsible for appointing members, but the committees themselves tend to forward names (Schuppli and Fraser, 2007). The UK's central ethics committee, the UK Ethics Committee Authority (UKECA), comprises the Secretary of State for Health and representatives from the National Assembly of Wales, the Scottish Ministers and the Department of Health (Hedgecoe, 2006) who are politicians. In South Africa, members of the NHREC are ministerial appointees (section 72, National Health Act). Membership of local RECs is determined by the respective institutions according to their individual policies.

The **political appointment of members to an REC** poses some challenges which could effect its integrity, independence and efficiency. It could also negate the multidisciplinary and multi-sector framework that is vital for good REC functioning (Van Bogaert and Tangwa, 2007). Politically sensitive research could in effect be censored because of the REC review process (Hamburger, 2004; Boronstein, 2007) as the committees would be vulnerable to political manipulation. Abuse of power in selectively choosing which research should be approved, coupled with a shortage of avenues for appeals against an REC decision, could stifle research (Boronstein, 2007).

In the case of some RECs, recruiting of members is by word of mouth (Schuppli and Fraser, 2007). This means that membership is open to people with various motives other than promoting the mandate of the REC (Schuppli and Fraser, 2007). Most REC members do not have a stipulated tenure. Low turnover of membership may stifle the introduction of new ideas, limit the possibility of new volunteer membership, and increase the risk of indoctrination (Schuppli and Fraser, 2007). Some senior faculty within institutions avoid serving on RECs as they feel constrained in exercising their autonomy because of the bureaucratic requirements of regulations governing RECs, which they perceive as focusing on unimportant minutiae (Fost and Levine, 2006).

FUNCTIONS OF RECS, APPLICATION AND APPEAL PROCESSES

The primary function of RECs is **participant protection** (Moodley and Myer, 2007; Kass *et al.*, 2007). This is derived from various rights accorded to humans, such as the right to freedom to participate or not in research, the right not to be harmed, deceived, or exploited, and the right to be treated with dignity and fairness, which are enshrined as basic tenets of biomedical research ethics (Van Bogaert and Tangwa, 2007). Besides participant protection, RECs are vital in demystifying health research by defining what is ethical for each application (Dixon-Woods *et al.*, 2007) and providing a public forum for the accountability of the researcher (Ikungura *et al.*, 2007). They serve as a third party which has the mandate to review and minimise conflict of interests (Kass *et al.*, 2007). Through what they say and what they do not say, the RECs act as a moral authority to structure the research environment (Dixon-Woods *et al.*, 2007). The SA Ethics Guidelines, 2004, propose that the functions of RECs include:

- a. **Review research proposals and protocols to ensure that research will be conducted in the spirit of endeavouring to promote health, and to prevent or cure disability and disease;**
- b. **Ensuring that humans involved in research are treated with dignity and that their well-being is not compromised;**

- c. **Ensuring that informed consent is obtained when enrolling a participant in the research;**
- d. **Granting approval where research proposals meet ethical standards.**

Different applications are treated differently, as the work of the REC is explicitly **judgment and discretion**. This differs from rule-based judgments, in which there is an appeal to a codified standard (Dixon-Woods *et al.*, 2007). In fact, if RECs bureaucratically and inflexibly apply regulations to all projects, their efforts could be corrosive to research and actually harm human subjects (Boronstein, 2007; Green *et al.*, 2006), because of a focus on minutiae at the expense of more important, substantive issues (Fost and Levine, 2007). Flexibility in application and interpretation of guidelines and standards could explain the occurrence of instances where a proposal is rejected by one REC and accepted by another, while apparently using the same guidelines (Cleaton-Jones, 2007). This flexibility in the application of regulations across RECs has been ascribed to differing conceptions of risk (Boronstein, 2007). This issue becomes highly problematic when multi-centre research proposals are considered. In Finland, variable practices of local ethics committees that caused extra work, delays and confusion to the applicants and made processes inefficient were reported as a disincentive to pharmaceutical companies who wished to carry out clinical studies (Keinonen *et al.*, 2003). Barriers to initiating clinical trials are in any case not uniform for all trials, as the steps involved in developing investigator-initiated, industry-sponsored, and cooperative group trials are all different (Govindarajan *et al.*, 2007).

Some **challenges inherent in REC functioning** include dissipation of resources, conflict of interests and delays, in addition to lack of experience and expertise (Pentz, 2004; Green *et al.*, 2006; Gherzi, 2004). Multi-centre research projects face additional problems which include multiple review processes, and additional costs and delays associated with administrative errors (Green *et al.*, 2006). Such difficulties, and the reported substantial variability of revisions requested by multiple RECs for a single research protocol, could present potential barriers to much-needed multi-institutional research (Dyrbye *et al.*, 2007).

A study on multi-centre research by Green *et al.* (2006) reported that the **time for REC approval** ranged from 52 days to 798 days, with a median time of 286 days at 43 sites for a full protocol review, and 127 to 546 days for an expedited review. In South Africa, the time from protocol submission to response was five weeks with a range of 10 days to 10 weeks (Moodley and Myer, 2007). The protocols reviewed included clinical and academic research. Clinical researchers feel that the long time frames for REC review processes for multi-centre research are prohibitive (Gheri, 2004). Others also feel that the REC review process might restructure research through multiple revisions in such a way that the nature of the inquiry is changed (Borinstein, 2007). The existence of cross-cultural issues in international inquiries could compound the delays that frequently occur with multi-centre research (Gheri, 2004). Bureaucracy poses further problems for developing nations where official meetings typically start late and deadlines are often ignored (Macpherson, 2004). Absenteeism from meetings by some REC members further adds to the delays, as some committees' decisions are influenced by variable attendance (Schuppli and Frazer, 2006). These hurdles raise fears among clinical researchers of diversion of their resources from patient care to research through futile REC applications (Macpherson, 2004). Some researchers have devised strategies to overcome persistent rejections by RECs, including several that may actually undermine their work (Lincoln and Tierney, 2004; Borinstein, 2007). Even if it may not be the intention of RECs to obstruct research, self-censorship by researchers in research avenues where obtaining approval is exceedingly difficult could have dire consequences, as important and much-needed research with policy implications may not be conducted (Borinstein, 2007).

The creation of a **central REC** to overcome multiple obstacles encountered by researchers seems reasonable. A centralised REC, through a versatile combination of centralisation, specialisation, and management, could expedite multi-centre research, lessen the workload involved for the submitter and also serve to coordinate study start-up at multiple sites across regions (Chaddah, 2008). On the other hand, yet another level of bureaucracy due to a centralised system of review may increase the burden on researchers and RECs (Gheri, 2004). A way of overcoming problems encountered by researchers would be

to adopt a system of expedited review like the one in Australia. There are three levels of review in the Australian system: there is no need for independent review of minimal-risk quality assurance; expedited review of low-risk quality assurance and other research; and full ethics committee review of higher risk research (Cave and Nichols, 2007). The drawback of this system lies in its dependency on the ability of the researcher or the REC to discern the mode of review suitable for the proposed research in each case. This may result in inadequate protection of research participants in a way that could jeopardise the future of clinical research, as participants may be less willing to engage in research processes (Campbell, 2004).

Funding of RECs

As medical research funding can yield a return of up to six-fold on investment through a healthier population that creates more wealth (Groves, 2008), **funding of RECs** is important to ensure greater returns from biomedical research while upholding public health and rights. In developing countries, research is often financed by well-resourced developed countries and conducted in vulnerable host communities with diverse cultural backgrounds (Milford *et al.*, 2006). Some RECs in Africa have no operating funds whatsoever, whereas others derive funding solely from either the government, foreign agencies, levying fees for reviews (Kass *et al.*, 2007), an affiliated university or institution, and/or pharmaceutical companies (Milford *et al.*, 2006: 2). Some RECs obtain their funding from a combination of these sources.

Although financial considerations should not take precedence over the mandate of protecting human subjects, the costs associated with reviewing protocols can be fairly significant (Hyman, 2007; Sugarman *et al.*, 2005; Boronstein, 2007). While recent legislative changes mandate ethical rigor, there are huge financial challenges to implementation, which is true even for resource-rich regions. Deficiencies in Institutional Review Board procedures have led to the suspension of several clinical trials programmes in the US, but strengthening the processes concerned has increased their operational costs substantially (Dhai, 2005).

In South Africa, funding of RECs is a constant problem at most institutions mostly because they are viewed as low-priority committees within the institutions (Moodley and Myer, 2007). Institutions provide varying levels of logistic support for their RECs (Cleaton-Jones, 2007) and it is fairly unlikely that any institution has sufficient resources available to meet the demand of having its RECs inspect comprehensively every form of research that involves human subjects. Fees levied for protocol review (only for sponsored protocols), are used to fund training in most of the RECs in South Africa (Moodley and Myer, 2007). Although adequate administrative support must be provided for the support, management and training of REC members (Ashcroft *et al.*, 2005), this is not a high priority for governments in developing countries which are struggling to provide health care and education services (Macpherson, 2004). Underfunding and/or understaffing of committees, or confining its members to poor systems and facilities could seriously undermine the credibility of RECs and their members (Van Bogaert and Tangwa, 2007) by making it difficult to attract the new members required to ensure fair representation from a wide range of professions and relevant community perspectives (Cleaton-Jones, 2007). Furthermore, the ability of RECs effectively to review protocols and to monitor approved research is compromised (Milford *et al.*, 2006). Research activity is quickly stifled through infrequent and indecisive REC meetings, which lead to delays in the initiation of projects. Inadequate monitoring of projects in turn undermines participant protections, which can be catastrophic for future research. Many funders (both governmental and private) from the US, Europe and Canada have stringent research ethics requirements, and lack of firm affirmation locally for research ethics through adequate support for and development of RECs may impact negatively on the ability of investigators to conduct internationally funded research (Rab *et al.*, 2008).

Various suggestions have been made to reduce the number of RECs, some of which meet too infrequently to be useful, and to have some RECs members serving as paid, full-time staff, for example retired senior clinicians (Ashcroft *et al.*, 2005). This is the case with the UK's National Research Ethics Advisors who operate on a continuous full-time basis so that straightforward studies can be approved without delay (Cave and Nichols, 2007).

REC workloads

The low current turnover of research proposals reviewed by local RECs has been attributed partly to **increased workloads** for the voluntary reviewers serving on these committees. Moodley and Myer (2007) found that between four and 30 protocols were reviewed per meeting. Cleaton-Jones and Vorster (2008) reported a 26% increase in total applications from 439 in 2003 to 553 in 2007 at the HREC of the University of the Witwatersrand, but there was a 16% reduction in industry-related clinical trial applications over the same period. Applications at the University of KwaZulu-Natal increased by almost 60% from 2000 to 2004 (Dhai, 2005). As in the case of other academic institutions, there was a 36% decline in the industry-related clinical research, while investigator-driven research increased by 72% over the same period. Similar trends have been observed in the UK, where applications doubled over a five-year period from 1991 to 1995. This increase in the workload has not, however, been paralleled by a similar increase in the membership and support of RECs, resulting in huge delays in review processes. This kind of situation has impacted negatively on researchers who try to meet publications deadlines, to earn tenure, or to conduct research that has strict time limits (Boronstein, 2007).

Monitoring and Oversight by RECs

The primary role of **monitoring and evaluation** of the ethics of clinical research is to champion the mandate of RECs, that is, to protect research participants. There are, however, other purposes achieved through this activity. Weijer (1995) held that the ultimate goal of any institution's commitment to monitoring research must be the education of its research staff and not to police researchers; this is a move towards evidence-based ethics, since a monitoring system is not an end in itself. Quality assessment and system improvement are achieved by the use of information generated from the monitoring exercise, and by determining whether guidance provided by RECs to researchers is actually being followed (Coleman and Bouësseau, 2008). Deviations by investigators from approved protocols can have grave consequences, both in terms of the safety of research participants and in public trust in the research

enterprise (Lavery *et al.*, 2004). The erosion of public trust may result in the reluctance of many patients to participate in clinical trials and in decreased funding for medical research generally (Wiejer *et al.*, 1995). **Ethical oversight of research** therefore serves as a public affirmation by RECs of their commitment to the ethical conduct of experimentation involving humans (Coleman and Bouësseau, 2008).

Despite the existence of regulations mandating RECs to monitor the research that they approve and the importance of continuing review, few RECs are in a position to honour this obligation (Weijer, 2001; Tuech *et al.*, 2005). Most RECs get assurance from the investigators' written reports that studies are being conducted in an ethical manner (Jamrozik, 2000). Only 18% of RECs were found to be performing 'ongoing reviews or audits' of research in a study conducted by the National Council on Ethics in Human Research in Canada (Weijer, 2001); 53% indicated that they required only an annual report from investigators. Another survey in ten Latin American countries revealed that 68% of the 25 RECs surveyed did not require progress reports from investigators, while 59% had no follow-up mechanisms in place (Rivera and Ezcurra, 2001). A survey of Australian RECs indicated that 44% 'always' or 'usually' undertook post-approval review and that, in almost all (99%) cases, this involved only annual reporting (Weijer *et al.*, 1995). Clinical trials by pharmaceutical companies in South Africa are closely monitored as part of good clinical practice, with the local RECs requiring the submission of six-monthly progress reports (Cleaton-Jones, 2002). RECs in South Africa do not perform active on-site monitoring of ethics, however, e.g. of the actual informed-consent processes. Much reliance is placed on the good faith and integrity of the researchers. It can be concluded that RECs in South Africa currently do not have enough support and capacity to comprehensively honour their post-approval responsibilities.

There are several guidelines for those aspects of research that require **monitoring**. These include: (i) continuing (annual or six-monthly) review; (ii) monitoring of the consent process; (iii) monitoring for adherence to protocol; and (iv) monitoring of data integrity (Article 8.9, SA-GCP, 2006; Article 4.7, Research Ethics Guidelines, 2004). The aim of monitoring includes quality

assurance in research (Lavery *et al.*, 2004). A study on monitoring clinical research at St Mary's Hospital Centre, Montreal, revealed flaws in the consent process: 3.8% of the consent forms used were different from the one approved, and there was a discrepancy between the age of participants and the age criteria specified in the protocol in 1.3% (McCuster, 2001). Deviation from the original research protocol without the approval of the RECs was reported in research by Weijer *et al.* (1995). It is obviously imperative that the ethics of research be monitored to safeguard both the participants and the clinical research enterprise itself. The enormous workload associated with monitoring as many as 1 500 projects per year, as is the case with the HREC of the University of the Witwatersrand (Cleaton-Jones and Vorster, 2008), remains a considerable challenge.

Recent amendments to the Helsinki Declaration leave little room to manoeuvre on the use of **placebos in clinical trials**. It states that "a new intervention must be tested against the best current proven intervention." A placebo is acceptable "where no current proven intervention exists" or where its use is necessary to determine an intervention's efficacy (Normile, 2008). The stringent stipulations of the Helsinki Declaration have resulted in the FDA allowing applicants for new drug approvals to bypass the Helsinki Declaration, and instead to comply with the ICH-CGP when conducting trials outside the US (Normile, 2008). This lack of universal uniformity in review standards creates inconsistencies in review processes that could harm the research enterprise. While the FDA's approach is less rigorous and more flexible and hence could facilitate research, there is a concern that this may be happening at the cost of compromising ethics.

ETHICAL PUBLICATION

There has recently been a serious re-examination of the ethics of publishing in the area of clinical trials, particularly in the US where a high incidence of '**sponsor control**' over authors has been uncovered, often extending to the unacknowledged drafting of manuscripts, or parts of manuscripts, by company staff. Failure to acknowledge sponsorships is another apparently

serious problem. Much attention is accordingly being given to signed '**conflict of interest**' statements required of all authors before publication.

While this has not yet been an issue in South Africa, careful attention needs to be given to the ethics of publishing, both within institutions and by regulatory bodies.

CONCLUDING REMARKS

Because clinical research is a social contract, ethical oversight is imperative as it is a public affirmation by RECs of their commitment to the ethical conduct of experimentation involving humans. Identifying and overcoming barriers to the successful conduct of research plays an important role in promoting and safeguarding the clinical research enterprise. Addressing the challenges at different levels in research in South Africa would assist in allowing clinical research to flourish.

Establishing new or strengthening existing programmes on research methods and ethics would be invaluable in promoting clinical research both at undergraduate and postgraduate levels. Incorporating ethics into research methodology would also be a major objective of any such programme.

Institutions and the Department of Health must support REC functioning both from an administrative and review perspective. RECs cannot continue to be viewed as committees with simple administrative functions. Where necessary, RECs should be able to carry out consultations with experts. Post-approval responsibilities, including passive and active monitoring of approved research by RECs, must also be adequately supported. Perhaps the time has also arrived for RECs to employ full-time, salaried reviewers, possibly drawn from the growing pool of retired experts.

Understanding and correctly implementing national and international regulations and guidelines by REC members serves to facilitate rather than hinder clinical research. Focused, ongoing educational programs for REC members on ethics protocol review, current and past ethics research discourse

and debate and ethics regulation are necessary to ensure competent, high-quality review, which should itself be subject to quality assurance at predetermined intervals.

Empirical research on REC functioning and the 'life-cycle' of clinical studies, from application for ethics review and clearance up to publication, is much needed, as is research and evaluation of ethics training curricula with regard to impact and implementation, at both researcher and REC levels.

Creation of a central REC to overcome multiple obstacles encountered by researchers in multi-centre projects is recommended. A centralised REC, through a versatile combination of centralisation, specialisation and management, could expedite multi-centre research, lessen the workloads of submitters and enable better coordination of study start-ups at multiple sites across regions (Chaddah, 2008). The role of the local RECs would then merely be to ensure that the research takes into consideration local nuances specific to the local context.

Adopting a system of expedited review for minimal-risk research could result in a significant reduction in the turn-around time for relatively innocuous studies.

FINDINGS

1. Research should be viewed as a social enterprise, i.e. a contract with society whereby ethically conducted research will serve to assure society that individuals will not be harmed.
2. The primary function of Research Ethics Committees (RECs) is thus the protection of research participants, including adequate scientific review for excellence and relevance.
3. The laws governing the conduct of research in South Africa are generally adequate, as are the institutional provisions for ethics governance and regulation. The National Health Act has set the standards for ethics

in research, but implementation of these standards is far from being realised.

4. While legislative changes have resulted in increasing numbers of research projects requiring ethics review and approval, there has not been a parallel increase of support for REC functioning, resulting in often unnecessary delays (this is particularly problematic regarding multi-centre studies).
5. Very few RECs are in a position to honour their obligations to monitor and provide oversight for the research they approve, despite the fact that the majority of REC members in South Africa are health scientists and clinicians and that RECs operate largely within university environments.
6. The shift of clinical trial commissioning from academic institutions to the private sector weakens the access of academic institutions to funding and their ability to develop research capacity.
7. Only a handful of core researchers are doing trials, and those that do conduct too many trials concurrently.

RECOMMENDATIONS

1. Institutions and the Department of Health must support RECs both from an administrative and review perspective.
2. This includes post-approval responsibilities, including passive and active monitoring of approved research; the monitoring and evaluation of REC functioning; and making information about clinical research more widely available.
3. The operational independence of the National Health Research Ethics Council should be maximised, while emphasising its overall accountability to government and society.

4. The National Health Research Ethics Council should register and accredit RECs and expedite their ability to process applications.
5. A system of expedited review for minimal risk research could result in a significant reduction in the overall turn-around time of study proposals.
6. Institutions and RECs should collaborate to reduce duplication in ethics review in South Africa and thus facilitate multi-centre studies.
7. Focused, ongoing educational programmes for existing and potential REC members on ethics protocol review, current and past ethics research discourse and debate, and ethics regulation are required to ensure competent, high-quality review, which should itself be subject to quality assurance at predetermined intervals.
8. Editors of journals publishing clinical research should maintain strict surveillance of conflicts of interest and inappropriate interference with publishing by sponsors.

REFERENCES FOR CHAPTER 5

- Aschcroft, R. E., Newson, A. J. and Benn, P. M. W. 2005. *Reforming research ethics committees: Latest proposals are a missed opportunity for a radical review.* *British Medical Journal.* 331 (17): 587-588.
- Baird, D. and van Niekerk, D. 2004. *The Regulation of Clinical Trials in South Africa.* *Quality Assurance Journal.* 8: 33-36.
- Boronstein, J. 2007. *The expanding purview: Institutional review boards and the review of human subjects research.* *Accountability in Research.* 15(3): 188-204.
- Campbell, E. G. 2004: *The future of institutional review boards: Concerns about IRBs in the enterprise of clinical research.* *Lancet Oncology.* 5(5): 327.
- Cave, E. and Nichols, E. 2007. *Clinical audit and reform of the UK research ethics review system.* *Theoretical Medicine and Bioethics.* 28(3): 181-203.
- Chaddah, M. R. 2008: *The Ontario Cancer Research Ethics Board: A central REB that works.* *Current Oncology.* 15(1): 49-52.
- Cleaton-Jones, P. 2002. *Monitoring of research: Is it practical or only a dream?* *South African Medical Journal.* 92(2): 127-128.

Cleaton-Jones, P. 2007. *Research ethics in South Africa: Putting the Mpumalanga case into context.* In: J. V. Lavery, C. Grady, E. R. Wahl and E. J. Emanuel (Eds.) *Ethical Issues in International Biomedical Research: A Casebook.* New York: Oxford University Press. pp 241-242.

Cleaton-Jones, P. and Voster, M. 2008. *Workload of a South African health research ethics committee in 2003 and 2007.* [Unpublished].

Coleman, C. H. and Bouësseau, M. 2008. How do we know that research ethics committees are working? The neglected role of outcomes assessment in research ethics review. *BMC Medical Ethics.* 8(6).

Department of Health (South Africa). 2004. *Ethics in Health Research: Principles, Structures and Processes.* Pretoria: Department of Health.

Department of Health (South Africa). 2006. *Guideline to good practice in the conduct of clinical trials with humans participants in South Africa.* Pretoria: Department of Health.

Dhai, A. 2005. Research ethics review – Protecting participants in research. *South African Medical Journal.* 95(8): 595-597.

Dixon-Wood, M., Angella, E., Ashcroft, R. E. and Bryman, A. 2007. Written work: The social functions of Research Ethics Committee letters. *Social Science & Medicine.* 65(4): 792-802.

Dyrbye, L. N., Thomas, M. R., Alex, J., Mechaber, A. J., Eacker, A., Harper, W., Massie, F. S., Power, D. V., Tait D. and Shanafelt, T. D. 2007. Medical education research and IRB review: An analysis and comparison of the IRB review process at six institutions. *Academic Medicine.* 82(7): 654-660.

Fost, N. and Levine, R. J. 2007. The dysregulation of regulation subjects research. *JAMA.* 298(18): 2196-2198.

Gherzi, D. 2004: The future of institutional review boards: Research ethics committees and the changing research environment. *Lancet Oncology.* 5(5): 325.

Global Clinical Trials Business Report & Analysis 2008–2018. Available at: http://www.pharmiweb.com/features/feature.asp?ROW_ID=1060.

Govindarajan, R., Young, J. W., Harless, C. L. and Hutchins, L. F. 2007. Barriers to clinical trials vary according to the type of trial and the institution. *Journal of Clinical Oncology.* 25(12): 1633-1634.

Green, L. A., Lowery, J. C., Kowalski, C. P. and Wyszewianski, L. 2006. Impact of institutional review board practice variation on observational health services research. *Health Research and Educational Trust.* 41(1): 214-230.

Groves, T. 2008. Stronger European medical research: Needs investment in people, not simply more money. *British Medical Journal.* 336: 341-342.

Gunsalus, C. K., Bruner, E. M, Burbules, N. C., Dash, L., Finkin, M., Greenough, W. T., Miller, G. A., Pratt, M. G., Iriye, M. and Aronson, D. 2006. *The Illinois White Paper — Improving the System for Protecting Human Subjects: Counteracting IRB Mission Creep.* Center for Advanced Study. Available at: <http://www.law.uiuc.edu/conferences/whitepaper/papers/>.

Hamburger, P. 2004. The new censorship: Institutional review boards. *The Supreme Court Review,* 343-350.

- Hedgecoe, A., Carvalho, F., Lobmayer, P. and Raka, F. 2006. Research ethics committees in Europe: Implementing the directive, respecting diversity. *Journal of Medical Ethics*. 32(8): 483-486.
- Hyman, D. A. 2007. Institutional review boards: Is this the least worst we can do? *Northwestern University Law Review: Symposium: Censorship and Institutional Review Boards*. 101(2): 752-757.
- Ikungura, J. K. B., Kruger, M. and Zaleke, W. 2007. Health research ethics. Review and needs of institutional ethics committees in Tanzania. *Tanzania Health Research Bulletin*. 9(3): 154-158.
- International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonized Tripartite Guideline. Guideline for Good Clinical Practice. 2006.
- Jamrozik, K. 2000. The case for a new system for oversight of research on human subjects. *Journal of Medical Ethics*. 26: 334-339.
- Kass, N. E., Hyder, A. A., Ajuwon, A., Appiah-Poku, J., Barsdorf, N., Elsayed, D. E., Mokhachane, M., Mupenda, B., Ndebele, P., Ndossi, G., Sikateyo, B., Tangwa, G. and Tindana, P. 2007. The structure and function of research ethics committees in Africa: A case study. *PLoS Medicine*. 4 (3): e136.
- Keinonen, T., Keränen, T., Klaukka, T., Saano, V., Ylitalo, P. and Enlund, H. 2003. Pharmaceutical industry's barriers and preferences to conduct clinical drug trials in Finland: A qualitative study. *European Journal of Pharmaceutical Sciences*. 20(1):35-42.
- Lavery, J. V., Van Laethem, M. L. P. and Slutsky, A. S. 2004. Monitoring and oversight in critical care research. *Critical Care*. 8(8): 403-405.
- Lincoln, Y. S. and Tierney, W. G. 2004. Qualitative research and institutional review boards. *Qualitative Inquiry*. 10(2): 219-234.
- Macpherson, C. C. 2004. The future of institutional review boards: IRBs in developing countries. *Lancet Oncology*. 5(5): 328.
- McCusker, J., Kruszewski, Z., Lacey, B. and Schiff, B. 2001. Monitoring clinical research: Report of one hospital's experience. *Canadian Association Medical Journal*. 164(9): 1321-1325.
- Milford, C., Wassenaar, D. and Slack, C. 2006. Resources and needs of research ethics committees In Africa: Preparations for HIV vaccine trials. *IRB Ethics and Human Research*. 28(2): 3-9.
- Moerman, C. J., Haafkens, J. A., Söderström, M., Rásky, É., Maguire, P., Maschewsky-Schneider, U., Norstedt, M., Hahn, D., Reinerth, H. and McKevitt, N. 2007. Gender equality in the work of local research ethics committees in Europe: A study of practice in five countries. *Journal of Medical Ethics*. 33: 107-112.
- Moodley, K. 2007. Teaching medical ethics to undergraduate students in post-apartheid South Africa, 2003–2006. *Journal of Medical Ethics*. 33: 673-677.
- Moodley, K., and Myer, L. 2007. Health research ethics committees in South Africa 12 years into democracy. *BMC Medical Ethics*. 8(1).
- Normile, D. 2008. Clinical trials guidelines at odds with US policy. *Science*. 322: 516.
- Patenaude, P., Grant, A. M., Xhignesse, M., Leblanc, F. and Courteau, J. 2008. Evaluation of clinical innovation: A gray zone in the ethics of modern clinical practice? *Journal of General Internal Medicine*. 23(1): 27-31.

- Pentz, R. 2004. The future of institutional review boards: Centralised IRBs. *Lancet Oncology*. 5(5): 327.
- Rab, A. M., Afzal, M., Abou-Zeid, A. and Silverman, H. 2008. Ethical practices for health research in the Eastern Mediterranean region of the World Health Organization: A retrospective data analysis. *PLoS Medicine*. 3(5): e2094.
- Reynolds, T. 2002. For institutional review boards, decisions can be subjective. *Journal of the National Cancer Institute*. 94(20): 1518-1520.
- Rivera, R. and Ezcurra, E. 2001. Composition and operation of selected research ethics review committees in Latin America. *IRB*. 23: 9-12.
- Scholtz, H. and Pretorius, S. 2005. Discovering South Africa. *Applied Clinical Trials*. Available at: <http://appliedclinicaltrialsonline.findpharma.com/appliedclinicaltrials/article/articleDetail.jsp?id=165485>.
- Schuppli, C. A. and Frazer, D. 2007. Factors influencing the effectiveness of research ethics committees. *Journal of Medical Ethics*. 33: 294-301.
- Sugarman, J., Getz, K., Speckman, J. L., Byrne, M. M., Gerson J. and Emanuel E. J. 2005. The cost of institutional review boards in academic medical centers. *New England Journal of Medicine*. 352(17): 1825.
- Tuech, J. J., Pessaux, P., Moutel, G., Thoma, V., Schraub, S. and Herve, C. 2005. Methodological quality and reporting of ethical requirements in phase III cancer trials. *Journal of Medical Ethics*. 31: 251-255.
- Van Bogaert, D. N. and Tangwa, G. 2007. Context, dual obligations and the vulnerability of independent review. In: J. V. Lavery, C. Grady, E. R. Wahl and E. J. Emanuel (Eds.), *Ethical Issues in International Biomedical Research: A Casebook*. New York: Oxford University Press. pp 238-239.
- Watson, R. 2007. Developing countries need stronger research guidelines. *British Medical Journal*. 334: 1076.
- Weijer, C. 2001. Continuing review of research approved by Canada research ethics boards. *Canadian Medical Association Journal*. 164(9): 1305-1306.
- Weijer, C., Shapiro, S., Fuks, A., Glass, K. C. and Skrutkowska, M. 1995. Monitoring clinical research: An obligation unfulfilled. *Canadian Medical Association Journal*. 152(12): 1973-1980.
- Whitney, S. N., Alcser, K., Schneider, C. E., McCullough, L. B., McGuire, A. L. and Volk, R. J. 2008. Principal investigator views of the IRB system. *International Journal of Medical Sciences*. 5(2): 68-72.

CHAPTER 6:

SCHOLARLY PUBLISHING AS A MEANS OF MEASURING AND
PROMOTING CLINICAL RESEARCH

In this chapter, we engage with the following questions:

1. What key problems with South African clinical research can be identified by an analysis of published outputs?
2. What specific interventions will best promote the overall productivity of clinical research in terms of both quality and quantity?

INTRODUCTION

Clinical research in a developing country has more than one purpose. It seeks to contribute to health care at all levels by identifying the causes of health problems, facilitating diagnosis, improving the efficiency and effectiveness of care, and promoting good policy-making. It supports the training of health professionals of all kinds, and contributes to global knowledge about the prevention and treatment disease. **Scholarly publication and the accompanying targeted dissemination of new information** is a key process in achieving these multiple functions, and is simultaneously an important, measurable indicator of its success in doing so (Gevers *et al.*, 2006). It must be remembered, however, that different functions require the use of available indicators in different, even if sometimes interdependent ways, and misleading impressions can be created if one publication indicator is applied to the exclusion of others.

Considerable importance is currently attached to **international publication** of local research. International publication has come to mean the placement of original articles in the relatively small number of journals selected to be indexed in international periodical databases. The most well-known and frequently analysed of these is the Thomson Reuters Institute of Scientific Information (ISI) database. With the enormous recent growth of publications (most of it in the developed countries), **specialisation within the main clinical sub-disciplines**, not to mention sub-sub-disciplines, has spawned in each of them a limited set of (mostly US and European) journals regarded as the most desirable and rewarding targets of researchers in that area. Thus, publishing 'internationally'

has come to mean publishing in the (usually voluminous) leading journals of each sub-discipline or sub-sub-discipline, achieving connectivity and reputation within the global community of other researchers working in a focused field, and satisfying the demands of funders and local policy-making for 'significant research outputs of high impact' (see below).

With this kind of publication, specialisation has given rise to a general migration of attention from the few remaining, still highly competitive **multidisciplinary clinical journals** to the many more and consequently larger-capacity **specialty journals** in the international indexes. If one considers the fabled categorisation of scholars into 'foxes' and 'hedgehogs' (the former constantly moving from one field to another, and the latter burrowing ever more deeply into one topic), the system has become much more friendly to hedgehogs than to foxes.

It is clear that the ability of researchers to publish articles arising from their clinical research in leading international speciality journals generally reflects high standards of design and execution of research projects, and promotes international collaborations, facilitates the acquisition of international grants and provides solid evidence for a variety of rewards in career development. It is generally considered that such publishing is a kind of visible iceberg or **proxy of general bottom-up excellence** in research groups, centres and institutions, in which in-house and local conferences provide opportunities for pre-publication presentation and concomitant peer review of productive work, apprentice-type development of younger staff and postgraduate students, and enhancement by collaboration (Mode 2 research) (Gibbons *et al.*, 1994). But the following questions can reasonably be asked: Are there are down sides to the prevailing system of formal publication almost exclusively in international speciality journals in a developing country such as South Africa? Do high-quality **local journals**, successfully completed **postgraduate studies**, effective **research-based teaching and training**, **innovation in drug development**, etc., also have specific roles and functions, other than being poorly visible components of the metaphoric 'iceberg of excellence' indicated by international publications? Is the scientific community too fragmented

to foster cross-field insights and collaboration? Can our young researchers develop into the leaders of tomorrow when they are located in isolated groups whose main scientific contacts and focus are outside the country? Can the core values of clinical research be acquired without community of purpose and enquiry?

We will accordingly examine whether and how the **worldwide trend of international specialty publishing is reflected in South African clinical research**, and how this affects the fact that clinical research has many important functions besides achieving recognition in the ways described above. We will look at the question of how analysis of published outputs helps us to assess whether and how the different functions are being met in an optimal and balanced manner. Specifically, we will endeavour to answer the question of how a health sector can be built that sees research as an essential element of improved health care. We will also address the question of how **research communities** can best be created, as part of a vibrant culture of clinical research, both for established practitioners and for new entrants to the field. Finally, this will connect to the matter of public engagement with clinical research.

While much of the information presented will be drawn from a **commissioned study** done for the Panel by the Centre for Research in Science and Technology (CREST) at Stellenbosch University (covering the ten-year period from 1996 to 2005), other published sources will also be extensively used.

MEASURING RESEARCH OUTPUTS

As already stated above, published research outputs in the form of **peer-reviewed scholarly journal articles** represent a powerful but not exclusive proxy for the performance of a research sector such as the clinical research sector in this country. **Books and book chapters, conference proceedings, patents and other published outputs** need, however, also to be considered, as disciplines vary in their use of these modalities. Published journal articles carry unique weight and simultaneously fulfil the five objectives of scholarly

publication in a consistent way: **registering, certifying, making aware, archiving and rewarding** (Roosendaal and Geurts, 1997).

Contributions to the **training and growth of young scholars**, and to the nature and quality of **health care service provision** (including safer and better drugs or therapies) are other potentially highly significant and valuable measures in the case of a sector such as clinical research (this topic is covered in other sections of the report).

SOUTH AFRICA'S PUBLICATION RECORD IN CLINICAL MEDICINE

South Africa is part of a 'long tail' of developing and least-developed countries that produce only a **tiny fraction of the world's health-research literature** (Paraje *et al.*, 2005). Despite this, the country is comparatively **a giant in sub-Saharan Africa**, and was for some time particularly productive, in world terms, in clinical medicine. In fact, health-related research has been responsible since the 1960s for the largest single contribution from South African addresses in the indexed **Thomson Reuters ISI** system. Tijssen's (2007) exhaustive study of African research articles included in Thomson Reuters' ISI indexes showed that 50% of all articles were in the medical and life sciences (the analogous figure for Africa overall was no less than 61%). In addition, an ISI-based citation assessment has revealed that no fewer than six South African universities exceeded a threshold set at 1% of all citations in 'clinical medicine' over the period 1995–2005, the only scientific field in which this was the case (Pouris, 2006). In 1995, it was reported in *Science* that Groote Schuur Hospital alone had achieved a greater number of the most cited 1% of the papers in the ISI system over the period 1981–1991 than all but two of South Africa's higher education institutions (Clery, 1995).

The above indicators of activity become more complex when newer analyses are taken into account. One study showed that the **share of total ISI-indexed papers** from South Africa in clinical medicine fell by 18%, from 0.59 to 0.48, between the periods 1990–1994 and 1996–2000, mostly caused

by growth in the size of the system with which it was not keeping up (Pouris, 2003). A more recent paper on the ISI databases found a slight fall in the absolute numbers of papers in this area published between 1996–2005 (7 342) and 1995–2004 (7 440), while the citations to South African clinical medicine papers increased from 50 462 (6.8 cites per article) to 55 500 (7.6 cites per article) (Jeenah and Pouris, 2008). The **citation rates** of South African papers in the field outperformed those of both India and Brazil, which are far bigger contributors in numbers of indexed papers. In terms of total indexed papers worldwide, however, South Africa ranked number 30 in clinical medicine, but number 20 in the geosciences (where only 2 594 papers were published that were indexed in the ISI system).

The data clearly show that the majority of the South African ISI-indexed papers in clinical medicine have in fact appeared in **international (overseas) speciality journals**, while the number of papers in this field in local journals, ISI-indexed or not, is small and has dramatically decreased in recent times. For example, the **number of controlled randomised trials** reported in the local flagship journal, the ISI-indexed *South African Medical Journal*, between 1976 and 1987 was 195, but fell to 92 between 1988 and 1997 (Pienaar *et al.*, 2003). Such trials are a crucial contributor to effective **translational research**, which has been promoted as a key priority by local policy-makers. (Much more information on clinical research publishing from and in South Africa is given below, arising from a study commissioned by the Panel.)

The composite picture of South African publications in clinical medicine/research is thus one of **continuing productivity** in the widely recognised publishing domain recorded in the international indexed ISI system, ranked second among the country's own broad scientific fields, but only thirtieth amongst all countries in this specific field. Since the average citation rates per article in clinical medicine exceed those of the principal emerging nations of the South, however, one could say the quality of South African papers according to this criterion has been higher and the quantity lower in a comparison with developing nations. In this sense, South Africa has performed like a **small developed country**, with a heavy focus on international journals

in the sub-disciplines or specialities, and very **little attention to local and/or traditional multidisciplinary publishing**, for which the decline of clinical research publications in the *South African Medical Journal* is the best indication.

Politically, the picture mirrors the still-continuing functioning of South African knowledge production as a (small) well-developed component co-existing within a much larger developing country. It must be emphasised that while there is no *a priori* reason why this should not be a satisfactory basis on which to build a future system of clinical research and its publication for the whole nation/society (see the above arguments in relation to the 'iceberg' model of proxy indicators of the all-round functionality of the research system), any recommendations for the future must be based on a careful examination of how the workings of such a (possibly declining) system will affect the development of the **next generation of clinical researchers**, and the achievement of a **vibrant national research culture** in an engaged society.

The above considerations induced the Panel to commission a detailed comparative study of all South African publications, in all health areas, that were accredited by the Department of Education (DoE) (ISI-indexed or not) over the ten-year period 1996 to 2005 (see below). This information permits a detailed review of **recent patterns of research article publication** within and from South Africa in bibliometric terms, in all ISI-indexed and non-indexed publications which were DoE accredited, with a view to discerning messages for a better future system. Outputs in the form of **books and book chapters** have also been reviewed in order to assess their nature and quality. Together, the findings can assist in the development of recommendations for enhancing multiple outputs and contributions of clinical research in South Africa in the future, as part of a general stimulation of the sector.

RESEARCH OUTPUTS IN THE FORM OF JOURNAL ARTICLES

As described in the 2006 ASSAf Report on journal-based scholarly publishing in South Africa (Gevers *et al.*, 2006), **quality assurance** takes effect at two levels. The first is the adoption of **best practice in editorial discretion and peer**

review when new articles are submitted to a journal; this limited and private assessment leads to acceptance or rejection decisions, improvements mandated by peer reviewers and/or editors, and copy editing to publication standard. The second takes place after publication, namely 'universal peer review in public', through **multiple citation** in other published articles in the literature, especially by authors completely independent of the original authors or groups (i.e. not self-citation) (Garfield, 1955). **Citation indexing** is by no means a perfect science, but it forms an important and valid part of bibliometric methodology provided its limitations are appreciated and necessary refinements applied when possible (e.g. field or journal-based normalisation to render comparisons more meaningful) (Moed, 2005).

The first 'either-in-or-out' stage confers **entry** of a research paper into the literature in a more-or-less standardised way; the second post-publication stage **positions** it in a general hierarchy of noteworthiness, which is a measure of its contribution to progress in a field being made by the vast community of scholars. The first measure is broadly one of **quantity** both as a total output and as a stratified one in terms of the kind of authorships involved (for example, inter-institutional or international collaborations, gender, race and age); the second measure is one of **quality**, and can also be refined, for example in terms of the pattern of appearance of citations over time. It is dangerous, however, to regard both measures as anything other than (significant) proxies for a more comprehensive evaluation of the productivity of a research system.

One must be aware of the **changing international background** to the research outputs of any one country. The continued rapid growth of the publishing system as a whole; the recent emergence of countries such as India, China, South Korea and Brazil as steadily increasing contributors; the continued skewing of the system in favour of English-language articles and journals published in Northern, wealthy countries; and the phenomenal intrusion of **Internet-based open access** into a previously print-based model, have all taken place in the same time-frame as the present analysis. For this reason, evaluative approaches that diminish the impact of system change

(such as determining the percentage of articles produced in a given period by a country as part of world production for that period) provide information that is just as significant as are absolute criteria (such as the number of papers produced by authors from a specific country in a given period). In any case, single parameter comparisons are highly suspect against a background of multiple contexts and a changing global system.

A COMMISSIONED STUDY

The Panel requested the **Centre for Research in Science and Technology (CREST)** at Stellenbosch University to carry out a study of research articles in the clinical and other health sciences published in journals both in South Africa and in other countries, over the period 1996 to 2005. The report prepared by CREST was received in February 2008, and has been adapted and extended in this section of the chapter; the data have been supplemented, where appropriate, with some derived from other sources.

The selection of appropriate methodology is crucial to the assessment of journal articles in a system; no single approach is adequate. CREST used its extensive '**SA Knowledgebase**' to produce a data set of **peer-reviewed articles in the health sciences** for the period concerned. SA Knowledgebase (SAK) is by far the largest database of research output in South Africa; it aims to deliver comprehensive, accurate and up-to-date information about article output from 1990 onwards. The database collects bibliographic information (excluding citations) on articles with South African author addresses which have appeared in journals accredited by the DoE. Information on the article title, article keywords, authorships, journal title, journal publishing detail and journal field in SAK is captured from two bibliographic indexes – the **Index of South African Periodicals (ISAP)** in Sabinet, and Thomson Reuter's **ISI** (usually now called the **Web of Science**). SAK includes all articles with a South African address appearing in the Web of Science and in, the case of ISAP/Sabinet, only articles appearing in a journal that has been accredited by the DoE.

Although the focus of SAK is on DoE-accredited journals, SAK is not limited to articles produced by the South African higher education sector. It also

includes, amongst others, articles produced by the science councils, national research facilities and government-based research institutions. The database also provides author-specific information by disaggregating the article output in terms of selected **demographic variables** (gender, race, year of birth, highest qualification and institutional affiliation).

At present SAK contains more than **115 000 journal articles published by 90 600 authors**, of which about 63 000 are South African authors. What makes SAK unique is that it includes biographic details about article authors, specifically their gender, race and age at time of publication (derived from birth year).

Fields and categories

For the purposes of this study, the CREST team extracted from SAK all articles published between 1996 and 2005 in journals that are classified within any of the 54 health-related journal field categories of ISI. These categories were re-classified by CREST into three broad fields: **clinical health sciences, basic health sciences and public/community health sciences**. Moreover, 35 journal field categories were classified within clinical health sciences, 12 within basic health sciences, and seven within public and community health sciences.

Not all journals were uniquely classified within a broad health field because multiple journal categories per journal applied. For instance, a journal could be classified by ISI as covering both toxicology and genetics/heredity, which would result in this journal being placed within both clinical health sciences and basic health sciences. (For this reason, the number of articles produced within the three broad fields cannot be added to produce the total number of articles in the sphere of health.)

The CREST dataset contained a total of 16 365 articles in health-related areas produced by South African authors between 1996 and 2005. Table 6.1 gives the breakdown of articles per year.

Table 6.1: Total number of health articles (CREST 2008)

Year	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005
Articles	1 208	1 415	1 447	1 574	1 877	1 778	1 758	1 864	1 790	1 654

Article production in the health sciences in South Africa

The overall output in all health science fields increased from 7 519 papers in the period 1996 to 2000, to 8 843 in the period 2001 to 2005. Although the number of papers in clinical fields increased between 1996 and 2002, the production of journal articles in clinical fields declined after 2003. The number of articles in basic health sciences and public/community health sciences remained more or less stable over the whole ten-year period (Table 6.2; Figure 6.1). In terms of the share of articles, by broad field that respectively appeared in overseas ISI journals (ISI & non-SA), local ISI journals (ISI & SA) and local journals not in ISI (Non-ISI & SA), only 38.5% of articles were published in South African journals (Table 6.3).

Table 6.2: Share of health articles produced by broad field, 1996–2000 and 2001–2005 compared

Fields	Number of articles			
	1996–2000	% of total of 7 519	2001–2005	% of total of 8 843
Clinical health sciences	5 679	75.5	6 313	71.4
Basic health sciences	1 795	23.9	2 307	26.1
Public/community health sciences	1 258	16.7	1 434	16.2
Total	7 519	--	8 843	--

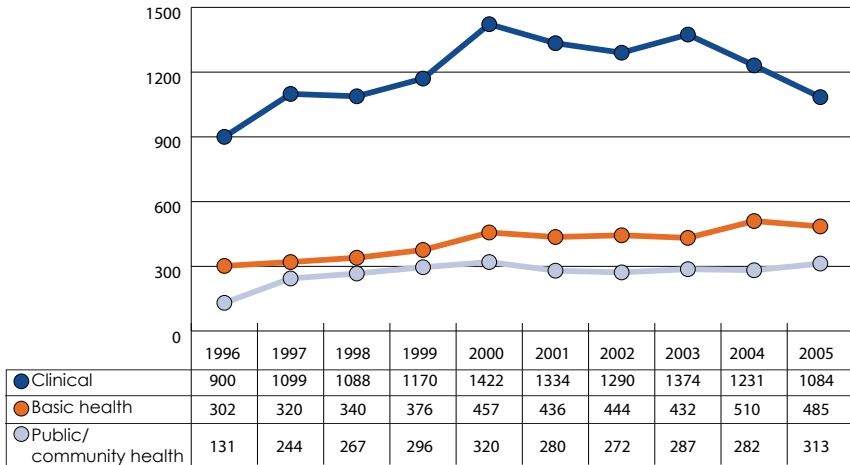


Figure 6.1: Trends in publication outputs in medicine, 1996–2005

Local research in the basic health sciences was published almost exclusively in overseas ISI journals (100% in 1996–2000 and 97% in 2001–2005). The 3% of publications in local non-ISI journals in 2001–2005 all appeared in *Current Allergy and Clinical Immunology*, a journal of the Allergy Society of South Africa (ALLSA).

The share of articles in overseas ISI journals in the clinical health sciences has been growing. This was happening partially at the expense of articles in local ISI journals (falling from 20% to only 18% between 1996–2000 and 2001–2005) but more at the expense of articles in local non-ISI journals (falling from 24% to 20%).

In public/community health sciences, the share of articles in foreign ISI journals has also been increasing (from 41% in 1996–2000 to 56% in 2001–2005). Concomitantly, there was a decrease in the share of articles in local non-ISI journals between these two time periods.

The breakdown in terms of journal 'index' category for each of the 54 journal field categories (hereafter called **sub-fields**) revealed the following trends:

Only in the fields of general & internal medicine and surgery did significant numbers of articles appear in **local ISI journals** (especially the **South African Medical Journal** and the **South African Journal of Surgery**). The shares of publications in these two journals remained constant between the two year-periods being compared (55% versus 56%, and 17% versus 19%).

Six sub-fields were characterised by a relatively large share of publications (>40%) in local non-ISI journals (according to figures for 2001–2005). Three of these were clinical disciplines: dentistry (72%), cardiac & cardiovascular systems (46%) and ophthalmology (43%). The others were classified as public and community health disciplines: health care sciences & services (72%), rehabilitation (70%) and nursing (69%).

In terms of the **average share of foreign and South African authors**, each by broad field and individual sub-field, the field of basic health sciences had the largest average share of foreign co-authors (29% in 2001–2005), while clinical health sciences had a share of 17% (see Table 6.3). There was an increase in foreign co-authorships in all three categories between the first and second five-year periods.

The following clinical fields reflected **above-average foreign co-authorship**: rheumatology (39%), haematology (38%), gastroenterology & hepatology (36%), oncology (33%), infectious diseases (32%), dermatology & venereal diseases (31%), peripheral vascular disease (30%), geriatrics & gerontology (29%), respiratory system (28%), emergency medicine (27%), allergy (26%), tropical medicine (26%), urology & nephrology (26%), medical informatics (26%), transplantation (25%), pharmacology & pharmacy (22%), psychiatry (21%), clinical neurology (21%), endocrinology & metabolism (21%) and obstetrics & gynaecology (19%).

Examination of the share of article **authors who were female** for the periods 1996–2000 and 2001–2005 reveals that progress has been best in the public/community health sciences (Table 6.3). In the public/community health sciences, 43% of the pool of researchers who published in 1996–2000 were female, and the figure increased to 48% during the period 2001–2005. The

share of female authors was somewhat lower in the clinical health sciences and the basic health sciences (33-36%), however.

Female authorship in all three main fields increased from 1996–2000 to 2001–2005 but the percentage point increases were on average between 3 and 5 points only.

The share of female authors in 2001–2005 was highest in three sub-fields of rehabilitation (75%), nursing (72%) and dermatology & venereal diseases (62%).

Table 6.3: Percentage of South African article authors who were female, by broad field – 1996-2000 and 2001-2005 compared

Fields	1996–2000		2001–2005	
	Total SA authors of known gender	% female authors	Total SA authors of known gender	% female authors
Clinical health sciences	2 429	33.2	2 454	35.9
Basic health sciences	1 227	34.8	1 388	36.7
Public/community health sciences	824	43.0	857	48.4
Total	3 056	35.7	3 253	38.5

Note: Totals do not add up because of multiple classifications of journals into journal field.

In terms of the **share of 'black' authors**, by broad field and sub-field, the following observations were made ('Black' was taken here to include Africans, 'coloureds' and persons with Indian origins) (Table 6.4):

Table 6.4: Percentage of South African article authors who were 'black', by broad field – 1996-2000 and 2001-2005 compared

Fields	1996–2000		2001–2005	
	Total SA authors of known race	% 'black' authors	Total SA authors of known race	% 'black' authors
Clinical health sciences	2 097	14.8	2 171	17.5
Basic health sciences	1 094	14.2	1 286	17.9
Public/community health sciences	722	14.4	783	20.8
Total	2 672	14.9	2 914	18.4

Note: Totals do not add up because of multiple classifications of journals into journal field categories.

During the period 1996–2000 14% of all authors in all three broad fields were 'black'. 'Black' representation increased in all fields over the next five years, although more so in public/community health sciences (from 14% to 21%) than in clinical or basic health sciences (an increase from around 14% to 18%). The average of 18% across all health science fields was significantly higher than the average of about 10% for all sciences in South Africa during the same period.

The three sub-fields with the largest percentages of 'black' authors during the period 2001–2005 were rheumatology (42%), anatomy & morphology (35%) and integrative & complementary medicine (31%).

In the case of the preceding gender and race analyses, each author appeared only once in the pool of researchers during any year-period because a person's gender and race status was taken to be 'fixed' – i.e. it could not change over time. In the case of an age analysis, however, a person's age category could vary within the same year-period (e.g. someone could be both 38 and 41 during 1996–2000, thus falling in both the 30–39 and 40–49 age categories in this period). Hence a different analysis was required to present the results in terms of the age of authors, that is, the share of article

equivalents (i.e. article fractions) produced by a particular age category over the two periods of comparison.

There was thus clear evidence of an **ageing publication workforce** in all fields examined. For the period 2001–2006, a substantial 13% of all authors in clinical science fields were over the age of 60. Two fields in particular – neuro-imaging (78% of authors in 2001–2005 older than 60%) and gastroenterology & hepatology (46% of authors in 2001–2005 older than 60%) – appear to be facing the biggest challenge in this area. Other fields in which more than 15% of the authors were older than 60 were: cardiac & cardiovascular systems, clinical neurology, dentistry, oral surgery & medicine, dermatology & venereal diseases, haematology, oncology, paediatrics, peripheral vascular disease, radiology, nuclear medicine & medical imaging, rheumatology and toxicology.

Citation analysis of health research published in, and from, South Africa

A number of bibliometric indicators of article output and citation impact were produced for this analysis by the **Centre for Science and Technology Studies (CWTS)** at the University of Leiden in Holland. It is important to emphasise that this analysis was done on all papers authored by at least one author with a South African address which appeared in one of the ISI citation indexes. This explains why the number of papers produced per field is not identical to the figures presented in Section 2 which also includes papers produced in South African (non-ISI) journals.

The overall production of ISI papers per field has increased: the **number of papers** in the vast majority of fields (33 fields) increased from the first period (1997–2001) to the second (2002–2006). The number of papers remained relatively stable in eight fields, whereas there was a decline in absolute number of papers in 13 fields.

Journal and field-normalised citation scores

We now turn to the two most robust and useful indicators produced by the CWTS analysis. The so-called ‘**crown**’ indicator that the CWTS at Leiden University produces – the **field-normalised citation rate**, signifies that the papers in a particular field have generated above-average recognition and visibility compared to all articles published in that field in a particular period. The following 18 fields (exactly one third of the 54 fields analysed) recorded above-average field-normalised citation rates for the period 2002–2006 (in descending order):

Table 6.5: Above-average field-normalised citation rates for the period 2002–2006 (in descending order)

Sub-field	Number of papers	Field-normalised citation rates, 2002–2006
Allergy	17	2.66
Orthopaedics	31	1.84
Anaesthesiology	64	1.62
Oncology	144	1.61
Infectious diseases	331	1.29
Psychiatry	128	1.20
Medical informatics	3	1.20
Integrative & complementary medicine	19	1.19
Tropical medicine	81	1.15
Paediatrics	191	1.11
Respiratory system	145	1.11
Critical care medicine	47	1.11
Cardiac & cardiovascular systems	90	1.10
Rheumatology	55	1.07
Health care sciences & services	35	1.07
Health policy & services	28	1.12
Immunology	243	1.04
Haematology	70	1.02

This is a very significant result, as in many of these cases these fields also improved their international visibility. Significantly, two of these fields are from public and community health, while none are from the basic health sciences and the remaining majority (16) are from the clinical health sciences.

Although some of these fields are extremely small (measured by number of papers), fields which produced more than 100 papers with an above-average field-normalised citation rate can be regarded as fairly robust and very visible sub-fields. These are oncology, infectious diseases, psychiatry, paediatrics, pulmonology and immunology.

With regard to **journal-normalised citation rates**, some fields showed an improvement between the two citation windows. These 23 fields were (again in descending order):

Table 6.6: Journal-normalised citation rates

Sub-field	Journal-normalised citation rates, 2002–2006
Allergy	2.04
Oncology	2.08
Orthopaedics	1.67
Anaesthesiology	1.62
Geriatrics & gerontology	1.46
Health care sciences & services	1.35
Health policy & services	1.35
Respiratory system	1.34
Medical informatics	1.34
Immunology	1.29
Paediatrics	1.29
Haematology	1.22
Critical care medicine	1.21
Rheumatology	1.19
Obstetrics & gynaecology	1.16
Infectious diseases	1.15
Tropical medicine	1.14
Medicine, general & internal	1.11
Medical laboratory technology	1.10

Sub-field	Journal-normalised citation rates, 2002–2006
Integrative & complementary medicine	1.08
Dermatology & venereal diseases	1.06
Virology	1.06
Otorhinolaryngology	1.04

The results for the **journal-normalised citation rates**, although not as revealing as the profiles of the field-normalised rate, are still valuable as they signify that nearly half of the fields in clinical research have recorded above-average journal-normalised citation rates for the period 2002 to 2006, and improved their international visibility in this process.

CONCLUSION: CREATING A VIBRANT LOCAL CULTURE OF CLINICAL RESEARCH

The above investigation of publication patterns in clinical and related health science fields has confirmed the increasing tendency of South African clinical researchers to publish their best work in 'international' journals, and particularly in a wide variety of specialty journals. The total number of 'clinical health sciences' articles published worldwide from South Africa every year has recently begun to decline, and much of the authorship is provided by an ageing cohort of established researchers. The few remaining health sciences journals have understandably migrated to a varying mix of first-submission original articles, summarised 'lectures' relating to continuing professional education, popular reviews, practitioner-directed features, house journal functions, a plethora of advertising, and articles repeatedly refused elsewhere. First-submission reports of good clinical research do not fit into this design, and so the country's productive clinical researchers live vicariously in the heavily North-oriented global system. **What this says about the local culture is that it is fragmented by specialisation and is heavily overseas-orientated. Such a system is poorly positioned to inspire a new generation of younger clinical scientists unless the previously described 'iceberg' effect, reflecting a well-functioning domain of intensive seminars, interdisciplinary collaboration, well-organised local conferences and exciting graduate programmes is actually**

operative. This kind of infrastructural health is unlikely given the well-recorded pressures on clinical researchers caused by increases in service pressures, administrative burdens and teaching responsibilities (partly due to the shrinking participation of part-time specialists as bedside tutors).

This report recommends elsewhere measures to address the optimisation of research training, development, multi-sector support and systemic policy change. In this section, only the topical issue of one or more local journals reporting original clinical research of high quality is raised.

We contend that a sufficiently large number of clinical research papers is produced every year to permit the operation of a local (or regional) journal dedicated to clinical research, if it is properly established, edited, supported and marketed, and is placed at the core of a reinvigorated clinical research community.

The *South African Medical Journal (SAMJ)* has an outstanding record as an internationally recognised, high-impact, general medical journal. It has, however, deliberately re-positioned itself in recent years as a mixed-content journal in which peer-reviewed articles constitute only about 20–25% of the total contents, and these are restricted editorially to articles which directly address health problems or are practically useful to general medical or public health practitioners. This approach has retained the interest of its readership. The infrequently appearing 'specialist daughter' journal titles of the SAMJ do not feature anything like the cream of the country's clinical research articles in their pages.

The 2006 ASSAf Report on *A Strategic Approach to Research Publishing in South Africa* made a strong general case for the publication of indigenous, high-quality journals, showcasing local activity and contributions, fostering coherence of the local research community, supporting the training of a new generation of high-quality researchers, and providing ample opportunities for intellectual growth of local scholars as editors, peer reviewers and contributors (Gevers *et al.*, 2006). Examples of successful (mostly open-access) journals in the clinical sciences can be found in India (e.g. *Indian Journal of Medical*

Research, MEDNOW), Brazil (*Brazilian Journal of Medical and Biological Research*), Mexico and China.

It is thus possible that enhancement of clinical research in South Africa will not be possible without a **'flagship journal'** published locally to the highest standards, promoting the coherence of the field, and visibly incentivising young researchers to develop to their fullest potential. The proposed journal could also sponsor **annual research conferences**, and be aligned with a **national society for clinical research**. The journal would need to seek indexing in the same international databases in which the SAMJ currently appears. In this way it would rapidly become an 'international journal' in the sense of promoting the reputations, rewards and funding opportunities of its published authors, while simultaneously enriching and enhancing the local clinical research community, especially its young members. Accreditation by the Department of Education in terms of its research outputs policy would automatically follow.

It is therefore reasonable to propose that the South African Medical Association (SAMA) be urgently requested to explore the possibility of publishing a new, open-access journal/daughter journal dedicated to high-quality clinical research, across the sub-disciplines in the field (*South African Journal of Clinical Research*). Alternatively, such a journal could be started independently through a joint initiative of interested stakeholders.

Such a journal should appear at least bi-monthly, and be edited by a competitively appointed, part-time, contract Editor-in-Chief, assisted by an appointed team of part-time, contract Associate Editors (including foreign-based clinical researchers of high standing), each responsible for particular selected sub-topic areas. The journal should maintain the highest possible standards, market itself energetically and professionally for article submissions and readership throughout Africa and the rest of the world, and contain added-value features such as editorial comment on key articles, authoritative reviews, scholarly correspondence, as well as accessible summaries and (English-language) formal abstracts of each article. Indexing in Thomson Reuters ISI, Medline and Google Scholar should be sought, and permission to authors to deposit their articles in institutional repositories granted.

The leading role of **multidisciplinary clinical journals** such as the *New England Journal of Medicine*, *The Lancet* and the *British Medical Journal* show that readers and contributors active in sub-specialties are ready to share their best work in high-quality periodicals, and, in turn, it is these which enrich their perspectives, generate fruitful collaborations and inspire young entrants to the otherwise daunting, uphill world of clinical research.

Multidisciplinary cohesion and synergy in the execution and reporting of high-quality research are also well-characterised features of successful departments and research units/centres/institutes. Extending this to larger contexts, in regional and even national concentrations of researchers, can be a highly effective way of increasing the productivity and impact of local teams, and of fostering a new generation of motivated and well-trained scholars. A modern journal that reflects the best thinking of the best clinical researchers, that is well-edited with sparkling enhancement features, and that becomes a regional flagship, is a prerequisite for such a vision.

FINDINGS

1. While South African scientific publishing represents a small fraction of world output, it comprises a large proportion of scientific research on the African continent.
2. Clinical research has formed an important part of South Africa's scientific output in terms of quality and quantity.
3. Although the number of clinical medicine journal articles has declined since 2003, nearly half of the fields in clinical research have recorded above-average field-normalised and journal-normalised citation rates for the period 2002 to 2006.
4. The trend has been towards increased publication of clinical medicine journal articles in international journals, and particularly in a wide variety of specialty journals.

4. Although more female and black authors have been publishing than before, progress has been slow and the proportion of older authors has been rising.

RECOMMENDATIONS

1. Promote publication of high-quality clinical research in local, especially multidisciplinary journals.
2. Change institutional cultures to promote local publication, for example by recognising and rewarding publication in both local and international journals of high quality.
3. Increase opportunities for local publication, for example through establishing vibrant supplements to existing journals and/or establishing a new, open-access, multidisciplinary journal for clinical research, possibly as a 'daughter' of the existing flagship, the **South African Medical Journal**.
4. Create a national society for clinical research.

REFERENCES FOR CHAPTER 6

Clery, D. 1995. *Elite science in a poor country*. *Science*. 268: 1282-1286.

Garfield, E. 1955. *Citation indexes to science: A new dimension in documentation through association of ideas*. *Science*. 122: 108-111.

Gevers, W., Mati, X., Pouris, A., Page-Shipp, R. and Hammes, M. 2006. *A Strategic Approach to Research Publishing in South Africa*. Pretoria: Academy of Science of South Africa.

Gibbons, M., Limoges, C., Nowotny, H. et al. 1994. *The New Production of Knowledge: The Dynamics of Science and Research in Contemporary Societies*. London: Sage.

Jeenah, M. and Pouris, A. 2008. *South African research in the context of Africa and globally*. *South African Journal of Science*. 104: 351-354.

Moed, H. 2005. *Citation analysis of scientific journals and journal impact measures*. *Current Science*, 89: 1990-1996.

Paraje, G., Sadana, R. and Karam, G. 2005. *Increasing international gaps in health-related publications*. *Science*. 308: 959-960.

Pienaar, E. D., Volmink, J., Zwarenstein, M. and Swingler, G. H. 2003. Randomised trials in the South African Medical Journal 1948-1997. *South African Medical Journal*. 92: 901-903.

Pouris, A. 2003. South Africa's research publication record: The last ten years. *South African Journal of Science*. 99: 425-428.

Pouris, A. 2006. The international performance of the South African academic institutions: A citation assessment. *Higher Education*. 54: 501-509.

Roosendaal, H. and Geurts, P. 1997. Forces and functions in scientific communication: An analysis of their interplay. Paper presented at the Conference on Cooperative Research Information Systems in Physics, 31 August — 4 September 1997, Oldenburg, Germany. Available at: <http://www.physik.uni-oldenburg.de/conferences/crisp97/roosendaal.html>.

Tijssen, J. W. 2007. Africa's contribution to the worldwide research literature: New analytical perspectives, trends, and performance indicators. *Scientometrics*. 71: 303-327.

CHAPTER 7:

EDUCATION AND SKILLS DEVELOPMENT – EQUIPPING
CLINICIANS-IN-TRAINING TO EMBRACE CLINICAL RESEARCH

In this chapter, we engage with the following questions:

1. How do we address the declining size and increasing age of the workforce actively engaged in clinical research?
2. How do we address the paucity of effective training programmes and unattractive career-pathing in the clinical research sector?

WHAT IS THE PROBLEM? DECLINING QUANTITY AND QUALITY OF RESEARCH OUTPUTS IN CLINICAL MEDICINE

An analysis of South African **research outputs in clinical areas** is presented in Chapter 6. What is directly relevant to this chapter is that there has been a decline in the contribution of the medical and health sciences from a 22% to a 20% share of overall South African production of ISI-indexed research articles (Department of Science and Technology, 2005), and an absolute fall in the number of papers in clinical medicine from 1 063 publications in 1987 to 736 in 2001. South Africa's share of the world's ISI-listed publications in clinical medicine declined by 22 from 0.59% (1990–1994) to 0.46% (1996–2000) (Pouris, 2003).

There are several factors that may be responsible for the falling number of outputs in clinical publications from South Africa. The two that are discussed below are **(1) the shrinking size of the health-research workforce, and (2), the absence of effective training programmes and suitable career paths for clinical researchers in South Africa.**

SHRINKING SIZE AND AGEING OF THE SCIENCE RESEARCH WORKFORCE

Research and development surveys of the DST have shown that the size of the public research and development workforce has been declining steadily since the early 1990s; a decline in full-time equivalent researchers of more than 40% (from nearly 6 000 to 3 424) between 1990/91 and 2001/2, has been

documented, affecting both the higher education sector and the science councils (Department of Science and Technology, 2005). Furthermore, the phenomenon of **ageing of publishing scientists** in South Africa continues unabated: whereas 18% of all articles by South African scientists in 1990 were published by authors over the age of 50 years, this percentage increased to 48% in 2002. Further analysis shows that these trends are not identical across scientific fields, but that the situation is worse for the medical and health sciences, possibly accounting for the reason for the decline in output (see Chapter 6).

ABSENCE OF A NATIONAL PLAN FOR THE EDUCATION, TRAINING AND EMPLOYMENT OF CLINICAL RESEARCHERS

There is no national plan for the education and training of clinical researchers in South Africa, despite its importance not only for the promotion of health in the South African public but also as a necessary catalyst of economic activity in one of the major missions of the government, the **'farmer to pharma'** programme of developing the potential of indigenous remedies for worldwide application, and becoming a major globally important centre of clinical trials activity.

The justifiably high priority given to primary health care in the national public health system has been allowed, inexplicably, to result in the **weakening of academic hospitals and tertiary facilities in the public sector**. This means small complements of professionals in specialist clinics, high service workloads, and poorly equipped facilities for diagnosis and treatment. At the same time, the **withdrawal of any kind of support for research (as opposed to service) by provincial health administrations, the refusal of the National Health Laboratory Service (NHLS) to discount fees for research projects, and the under-funding of the MRC** in respect of its resulting 'sole mandate' for research support in the clinical area, have amounted to a massive disinvestment by the state in clinical research activity.

The above situation has been addressed in part by the recent decision to provide significant funds to health science faculties via the Department of Education (DoE) for **clinical training at both undergraduate and postgraduate**

levels (I. A. Bunting, DoE, Personal communication, 2008). In the 2007/08 to 2009/10 national budgets, the National Treasury allocated funds for the first time to the DoE for the clinical training of health sciences professionals. The amounts involved were: 2007/08: R8 million to fund a review of clinical training in the health sciences; 2008/09: R200 million to support clinical training in universities; and 2009/10: R300 million to support clinical training in universities. In March 2007, the Director-General of the then Department of Education established a committee to undertake the review referred to above. This review committee had as chair the Deputy Director-General: Higher Education, and as members officials from the Departments of Education, Finance and Health, and representatives from the Health Sciences Professional Council and from Higher Education. The review committee was set four broad tasks:

- (1) to examine the current financial arrangements which hold between provincial health departments and higher education institutions;
- (2) to investigate the clinical training needs of higher education institutions;
- (3) to examine the current student-carrying capacity of health sciences faculties, and consider ways in which this capacity could be increased;
- (4) to determine how the 2008/09 and 2009/10 allocations for clinical training should be distributed between universities.

The uses to which these allocations could be put included the appointment of additional clinical training staff and other staff to support the delivery of clinical training services, support of partnership agreements with public and/or private providers of clinical training services, meeting operating costs of clinical training service delivery, and improving the infrastructure needed for clinical training, including equipment, building refurbishment, and the construction of new clinical training facilities. Allocations were provided when detailed spending plans had been submitted and approved. Progress reports were required.

The mechanism **distribution of the clinical training funds** (R500 million in 2008/09 and 2009/10) proposed by the official working group was based on a simple formula. All programmes which had clinical training requirements were included, mainly undergraduate degree programmes in medicine, dentistry, physiotherapy, occupational therapy, pharmacy, speech pathology, audiology, dietetics, dental therapy, as well as master's-level specialist training programmes in medicine, surgery and dentistry. These degree programmes were assigned, for each year of study, a weighting which represented the proportion of the curriculum for that year devoted to clinical training. These weightings were applied to the 2006 head count student enrolment in the programmes which qualify for clinical training funding. (These head count enrolment totals had to be supported by a certificate from each institution's external auditors). The weighted totals of undergraduate and postgraduate clinical training students were aggregated into a total for each institution, and ultimately a weighted national total. The allocation each institution received was then determined as:

$(\text{institutional weighted total} / \text{national weighted total}) * \text{funds available}.$

It is evident that this highly significant intervention in clinical training, approved and funded in 2008, interfaces directly with the subject of clinical research training, and presents a model which could produce massive improvements in the quality and quantity of South African clinical research as advocated in this report. There is already a possibility that the funding of research/research training in the case of MMed candidates could be funded under the scheme as it is currently set up.

DEGREE STRUCTURES PROMOTING RESEARCH TRAINING AND DEVELOPMENT

Intercalated BSc degrees in medical sciences are available in most South African medical schools, and in the past have served to induct promising individuals into the research in this area. They have, however, been seen by most faculties as minor programmes for the gratification of the personal interest

of a small number of gifted students, and as rather costly, and certainly not as deliberately planned pathways to develop a new generation of research-active clinicians (but see international example below).

The **BScMed Honours programmes** offered in various special directions by most health science faculties are generally open to medically qualified students, but the take-up has been very low in recent years, associated with the extensions of compulsory community service, high student indebtedness, and the lack of adequate bursaries at the level concerned.

The **Master of Medicine (MMed) degree** is offered by the eight South African universities with programmes leading to the MB ChB degree and related postgraduate programmes. It is one of the pathways to registration as a specialist in South Africa, but serves mainly as a professional qualification – its relatively minor research component generally does not result in the initiation or production of high-quality research, nor is there frequently significant continuation of research activity after registration. In fact, several universities for many years tacitly registered students for the MMed degree only to allow them to complete their College examinations and default on completing the master's degree (registered by the Department of Education as 'drop outs'). The Health Professions Council of South Africa (HPCSA), the authority that sets the standards of training and requirements for registration of doctors, is proposing to make the completion of a research component a condition for registration of specialists in South Africa. This initiative offers an opportunity to turn the research component of the MMed degree into programmes to develop properly equipped clinical researchers, for example by combining them with honours work offered by the same institution and faculty.

There is little incentive for clinicians to train in **doctoral programmes**, resulting in a very small number of the clinical professoriate having doctoral degrees. No equivalent of the MD/PhD programme which is so active in the US has yet been developed in South Africa into analogous MB ChB/PhD programmes (see below), where purist interpretations of both the standardised undergraduate curriculum and the 'very senior' PhD degree have conspired to make the pursuit of doctoral degrees specially ambitious and rare. Financial support packages at this level are also not readily available.

While the above situation in respect of formal postgraduate studies in clinical research provides many reasons for declining numbers of clinical researchers and declining outputs, it is likely that the problem begins much earlier, in the approach to the undergraduate phase of development.

STATUS OF CLINICAL TEACHING AT UNDERGRADUATE LEVEL

Medical research is an **integral part of medical education** (Deo, 2008), hence the need to promote a research culture at undergraduate level. Universities in the US admit only postgraduates to clinical study, thus ensuring that a wide range of majors already completed serve as the foundation of a research system able to capitalise on the same diversity of developed skills (in this country, only the University of the Witwatersrand offers this kind of curricular organisation). Most South African universities offer undergraduate medical programmes that in recent years have been significantly modified and broadened in line with the premises of 'primary health care'. This has had both good and bad effects, seen from the point of view specifically of clinical research capacity – on the one hand, the student-centredness of the curriculum has fostered independent thought and personal development, on the other, grounding in formal 'preclinical' scientific disciplines has been diluted and weakened.

Despite these changes in undergraduate curricula, most faculties have programmes that sensitise undergraduate students to the concept of evidence-based medicine and research. As an example, at one university, medical students in their third and fourth years are exposed to various aspects of research through lectures and theme sessions, looking at different types of studies, research methods, study designs, systematic reviews and meta-analysis, during a total of 15 two-hour sessions and 11 two-hour sessions, respectively. The students also undergo formal teaching in research protocols, methodology, questionnaire design, statistics and data analysis in their fifth year, with a contact time of over eight hours. There are also research days (a total of five complete days per year) where students in groups draft a protocol

and carry out empirical research after its approval. The research project contributes to 35% of the year mark for the students' integrated block.

At the University of Cape Town, there is a compulsory four-week long supervised special study module (SSM). During this period, students choose from about 100 research topics provided by the Department of Medicine. They have no other course commitments during this time, hence the four weeks are devoted to various research activities including literature reviews, actual conduct of a study and audits. It is mandatory that students are successful (pass) in this component prior to progressing to the next semester.

At the University of Pretoria, ethics training forms part of the 'Golden Threads' of the curriculum, and is addressed in all of the six years of study, culminating in an 'Ethics Breakaway' in the final year, with mandatory attendance. Clinical research is promoted in all years, and even in Year 2 students do small collaborative research projects to be presented to the class. Clinical trials are addressed in all clinical blocks as 'Evidence-Based Medicine' (another 'Golden Thread' of the curriculum). Drug trials are mentioned but less thoroughly addressed. Specific matters, including scientific misconduct, are addressed during many blocks and in particular during a special activity comprising six to 10 teaching hours in the block called 'Evidence-Based Medicine'.

At the University of the Witwatersrand, medical students in the third and fourth years of study are exposed to various aspects of research through lectures and theme sessions. During these guided sessions, they review published articles, and look at different types of studies, research methods, study designs, systematic reviews and meta-analyses. In 2008, third-year students had a total of 15 two-hour sessions and fourth-year students had a total of 11 two-hour sessions specific to research. These students further underwent formal teaching in research protocols, methodology, questionnaire design, statistics and data analysis in their fifth year of study. In 2008, the total contact time for the fifth-year students was 8,5 hours. Furthermore, there are research days (a total of five complete days per year) where students in groups draft a protocol to conduct an empirical research project after approval of the protocol. This research project contributes to 35% of the year mark for the students' integrated block.

SUPPORT STRUCTURES FOR RESEARCH WITHIN INSTITUTIONS

Research flourishes in an environment that is conducive for research. Inspirational visions and missions aid in fostering a culture among students that reflects the ethos identified in the visions and missions. Research management at institutions of higher learning has an impact on the volume and quality of research output. Early-career researchers (young researchers) need a nurturing environment and a system of support in the early stages of their career.

A **web-based survey of South African universities with medical schools** was conducted to identify components that foster a rich research environment, and structures that promote and support research at these institutions. Special attention was given to (i) whether research was mentioned in their mission and vision statements, (ii) the existence of a research strategic plan, (ii) existence of a research office that offers various services such as research grants facilitation, monitoring and assisting young researchers, and (iv) the existence of information on research that is easily accessible to researchers, e.g. research links on the websites.

Table 7.1: Website survey of research support structures in South African universities with medical schools

	Research mentioned in the vision statement	Research mentioned in the mission statement	Existence of a research strategic plan	Existence of a research office	Research website link
Free State University	Research not mentioned in the vision statement	"The pursuit of scholarship as embodied in the creation, integration, application and transmission of knowledge by promoting the following within the ambit of financial sustainability: Pure and applied research"	A Strategic Framework for the Development of Research at the University of the Free State (2003)	Exists as: Research Development Directorate	Available at: http://www.uovs.ac.za
Medunsa University	Not available on the website	"A world-class African university which responds to education, research and community development needs through partnerships and knowledge generation – continuing the long tradition of empowerment"	Not available on the website	Exists: Research Administration Office	Available at: http://www.medunsa.ac.za/research/welcome.htm
Stellenbosch University	"In a spirit of academic freedom and of the universal quest for truth and knowledge, the University as an academic institution sets itself the aim, through critical and rational thought, of gaining national and international standing by means of its research outputs"	Research not mentioned in the mission statement	Research strategy contained in the university's Strategic Framework for the Turn of the Century and Beyond (2000)	Research Development and Support Division	Available at: http://www.sun.ac.za

	Research mentioned in the vision statement	Research mentioned in the mission statement	Existence of a research strategic plan	Existence of a research office	Research website link
University of Cape Town	Research not mentioned in the vision statement	<p>"Our mission is to be an outstanding teaching and research university, educating for life and addressing the challenges facing our society.</p> <p>Educating for life means that our educational process must provide: research-based teaching and learning"</p>	University of Cape Town Research Strategy	Research office exists under The Department of Research and Innovation	Available at: http://www.uct.ac.za/research/libraries
University of KwaZulu-Natal	Research not mentioned in the university's vision statement but mentioned in the faculty of health sciences vision statement (Strategic Plan 2008)	"A truly South African university that is academically excellent, innovative in research, critically engaged with society and demographically representative, redressing the disadvantages, inequities and imbalances of the past"	Research Policy II: Developing, Retaining and Rewarding Researchers (2008) and Strategic Plan - Faculty of Health Sciences (2008)	Exists: Research Office	Available at: http://www.research.ukzn.ac.za
University of Pretoria	Research not mentioned in the vision statement	"The mission of the University of Pretoria is to be an internationally recognised South African teaching and research university and a member of the international community of scholarly institutions that: encourages academically rigorous and socially meaningful research, particularly in fields relevant to emerging economies"	Exists as one of the thrust areas in the Innovation Generation: Creating the Future, 2007-2011 Strategic Plan	Research Office in the Department of Research Support	Available at: http://www.web.up.ac.za

	Research mentioned in the vision statement	Research mentioned in the mission statement	Existence of a research strategic plan	Existence of a research office	Research website link
University of the Witwatersrand	<p>"Universities have the immense responsibility of producing cutting edge research..."</p> <p>"We will build increasingly close relationships with the private sector, and the public sector professions in seeking sponsorship of research projects, research students, joint appointments of staff, and joint programmes of research that contribute to economic and academic development."</p>	"Wits' mission is to build on this foundation in a way that takes account of its responsibilities within South Africa today; and to maintain and enhance its position as a leading university in the Republic, in Africa, and in the world by sustaining globally competitive standards of excellence in learning, teaching and research."	University of the Witwatersrand Strategic Research Plan 2007 to 2011	Exists: Research Office	Available at: http://www.web.wits.ac.za/Academic/Research
Walter Sisulu University	"Walter Sisulu University (WSU) will be a leading African comprehensive university focusing on innovative educational, research and community partnership programmes that are responsive to local, regional, national development priorities, and cognisant of continental and international imperatives."	"In pursuit of its vision as a developmental university, WSU will: maintain the highest possible standards in innovative teaching and learnerships, basic and applied research, community development partnerships in cooperation with development agencies, the public and private sectors ..."	Not available on the website	Not mentioned on the website	Not available on the website

While research is mentioned in only three of the vision statements of eight universities, it has been identified as an important mission in all but one of the universities. Six of the eight universities either had a strategic plan specifically for research, or research was enshrined in the strategic plan available on their respective websites.

RESEARCH ETHICS TRAINING IN SOUTH AFRICA

There are a number of **institutional research ethics training programmes** in the country for both researchers and research ethics committee members.

South Africa has two Fogarty-funded programmes: International Research Ethics Network for Southern Africa (IRENSA) based in Cape Town and the South African Research Ethics Initiative (SARETI), a collaboration between the Universities of Pretoria and KwaZulu-Natal. The University of the Witwatersrand runs a master's programme in Bioethics and Health Law, which includes an elective unit in research ethics. Several institutions conduct short workshop-style courses in ethics in research. In addition, the University of Stellenbosch has recently developed an online programme for advanced Good Clinical Practice (GCP) training in research.

These programmes and courses contribute significantly to capacity building in ethics in research in the country, and multidisciplinary expertise and leadership in research ethics and bioethics is being developed. An objective of most programmes is the building of capacity for ethical review of health research and strengthening of institutional training capacity necessary to achieve this.

INTERNATIONAL POLICY AND PLANNING INITIATIVES THAT SEEK TO ADDRESS THE PROBLEM

Two examples of programmes in clinical medicine in other countries that are designed to produce clinical researchers as their major outcome are worth considering at this point: (a) intercalated degrees in the UK system, and (b) the MD/PhD programmes in many US universities.

Intercalated degrees in the UK medical schools

As opposed to the tiny proportion of South African medical students who choose this option, about one third of medical students in the UK add an additional year to the basic five-year undergraduate course and intercalate a degree in medical science (a BSc or BMedSci) (McManus *et al.*, 1999). The UK Medical Research Council has concluded that the intercalated degree is extremely valuable in introducing future clinicians to research, and in providing a cadre of graduates who are likely to become attracted to, and excel in, a career in academic medicine (Smith, 1986). A longitudinal study of final-year medical students who had taken intercalated degrees has provided evidence that they were more interested in medical research than their comparators, and had better 'deep and strategic style' scores. The effects of the intercalated degree were greatest in medical schools where a relatively small proportion of students took the degree; differences between medical schools are most easily explained by resource dilution (McManus *et al.*, 1999).

The barriers to expansion of intercalated years in the South African situation are financial (additional costs to both funders/sponsors and families), social (cohort cohesion), and academic (extra costs of intense supervision in scientific disciplines). These barriers could obviously be lowered if prioritised plans were carefully developed and adapted to local conditions. For example, exemption from one year of compulsory community service on successful completion of an intercalated degree would have little effect on national health person power but a big effect on research capacity development.

Among the systemic enablers of researcher development, two deserve special mention. The first, discussed in Chapter 6 with a firm proposal for remediation, is the existence of a high-quality local journal for clinical research which is multidisciplinary and so designed that it encourages broad reading and 'lateral' learning amongst most or all people who are active in research in the country, young or established. The second is concentration on local conferences to make them hothouses for presentation skills, networking, collaborations and generally 'getting the hang of it'. Again, multidisciplinary conferences are important even though 'deep-focused' workshops and conferences can also be valuable when participative attendance is encouraged and skill-enabling objectives are built into the design of their programmes.

MD/PhD Programmes in US and UK universities – a high-powered model for the development of a medical research workforce

Joint MD/PhD programmes are offered at nearly every US medical school in a wide range of fields. Many MD/PhD programmes receive institutional support through the Medical Scientist Training Program (MSTP) of the National Institute for General Medical Sciences of the National Institutes of Health (NIH). The primary intent of these joint MD/PhD degree programmes is to produce highly trained physician-scientists who will engage in biomedical science research careers.

A report of the MSTP cohorts enrolled between 1970 and 1990 revealed that MSTP graduates were more likely than other medical school graduates to receive postdoctoral fellowships, to hold academic appointments, to receive external research funds, to apply for NIH grants, and to have published more than their MD counterparts (Rosenberg, 2008).

It is worth noting that Cambridge and other universities in the UK now also offer the equivalent degree of MB/PhD, which may be more suited to our medical curriculum which is based on the British model. The Cambridge website describes the degree as follows:

The MB/PhD Programme leads to the MB, BChir and PhD degrees and is designed for medical students who are interested in academic or research careers by enabling them to integrate a three-year period of research with their clinical education.

The clinical component of the curriculum is designed to equip students for a lifetime of medical practice in a changing world with emphasis on the acquisition of clinical skills by direct patient contact. At the start of the programme, students follow the Standard Course Stage 1 curriculum up to and including the Stage 1 student-selected component. Following a clinical academic module and subject to satisfactory progress, this is followed by a three-year period of full-time research combined with three hours a week of clinical education. It concludes with students rejoining the clinical course to complete their studies with either the Standard or Cambridge Graduate courses, depending upon the time of completion of the PhD.

As in the case of intercalated degrees, a **national MB ChB/PhD programme** would have to be adequately resourced and adapted to local conditions. The many BScMed honours programmes already available could readily become 'qualifying courses' for concurrent and subsequent hands-on research leading to PhD degrees – this effectively spreads the load of development work between non-clinical and clinical staff, and establishes sustained networks of personal support and encouragement amongst both ex-students and their teachers.

Experience in certain countries, notably the UK, has indicated that concurrent MB ChB and PhD/M studies can cause some students to 'fall between two stools', and it is probably necessary in each instance to ensure that mentoring takes place to avoid such situations. A flexible approach to career development is absolutely necessary in relation to the challenging issues confronting individual students/trainees.

LOCAL POLICY AND PLANNING INITIATIVES THAT SEEK TO ADDRESS THE PROBLEM

Department of Health: The National Human Resources Plan for Health of 2006

The National Human Resources Plan for Health that was launched by the National Department of Health in 2006 recognises the general shortage of health professionals in South Africa, and has identified a number of priority areas for implementation. The plan calls for the establishment of a Health Sciences Academic Development Programme that is spearheaded at the national level and implemented at the institutional level to:

1. Develop health sciences educators;
2. Recruit and increase the pool of health sciences academics;
3. Promote research;

4. Bring about demographic transformation of the academic leadership cadre and specialists in the country.

The next step in this process is intended to be the development of a strategy and associated implementation process, which may be assisted by the present report.

The Colleges of Medicine of South Africa Project – 2007

The Colleges of Medicine of South Africa (CMSA) convened a **Policy Forum on Tertiary Academic Medicine and Specialist Training** on 24–25 October 2007 and again on 1–2 December 2008. The aim of the Forum was to bring together leaders, policy-makers, decision makers and stakeholders to discuss strategic issues with regard to tertiary academic medicine and specialist training in South Africa. The output from the event was an agreement to continue to create a forum for discussion and debate on issues relevant to academic medicine and specialist training; a memorandum was sent to relevant government departments informing them of the CMSA initiative to improve specialist and sub-specialist training.

Department of Science and Technology's Ten-year Innovation Plan – 2008

The purpose of the **DST's Ten-Year Innovation Plan**, which was published in 2008, is to develop a knowledge-based economy in which the production and dissemination of knowledge leads to economic benefits and enriches all fields of human endeavour. The Plan identifies four pillars for progress:

1. Human capital development;
2. Knowledge generation and exploitation (R&D);
3. Knowledge infrastructure;

4. Enablers to address the 'innovation chasm' between research results and socioeconomic outcomes.

One of the **five grand challenges** to act as the substrate for research and development is the '**Farmer to Pharma**' value chain to strengthen the bio-economy. Over the next decade, South Africa is urged to become a world leader in biotechnology and pharmaceuticals, based on the country's unique indigenous resources. To succeed in this area, South Africa will need to produce an expanded pool of appropriately trained clinical researchers. Indeed, the ten-year plan recognises that a significant strengthening of the production of human capital and improvement of the institutional environment for knowledge generation is necessary to achieve its goals.

The targets for this human capital development programme over the next 10 years are as follows:

1. Five hundred Research Chairs by 2018 (70 in place by 2008);
2. About 6 000 PhDs produced per year in all science, engineering and technology disciplines by 2018 (currently 600 per year are produced).

FINDINGS

1. The clinical research force is ageing and has also been steadily declining in numbers since the early 1990s.
2. The combined burden of clinical teaching and training, health service, and research thus falls on a shrinking and ageing pool of academics in health science faculties.
3. This means that there is limited capacity to increase the production of properly trained health care workers and to train and inspire a new generation of clinical researchers.

4. Simultaneously, the situation has brought about an inability to cope with the increasing demands of clinical service imposed by the colliding epidemics of infectious disease (TB and HIV/AIDS) and non-communicable disease (heart disease and stroke).
5. A national plan involving the spending over three years of half-a-billion rand has recently been implemented to enhance clinical training at all levels in South African higher education institutions
6. There is, by contrast, currently no national plan to provide coordinated support for the training and development of clinical researchers, and grossly insufficient support for research professorships and training fellowships in the clinical research field.
7. There is little incentive for clinicians to train in doctoral programmes, resulting in a very small number of the clinical professoriate having doctoral degrees.
8. There are a number of institutional research ethics training programmes in the country for both researchers and research ethics committee members.
9. The National Human Resources Plan for Health that was launched by the National Department of Health in 2006 recognises the general shortage of health professionals in South Africa, and has identified a number of priority areas for implementation.
10. The Colleges of Medicine of South Africa (CMSA) has a Policy Forum on Tertiary Academic Medicine and Specialist Training.
11. The DST's Ten-Year Innovation Plan aims to develop a knowledge-based economy in which the production and dissemination of knowledge leads to economic benefits and enriches all fields of human endeavour.

RECOMMENDATIONS

1. **Create a national plan for research capacity development in clinical sciences** (a 'National Clinical Scholars Programme') for undergraduate and postgraduate students, and junior and senior faculty in clinical research, based on the idea of the PhD as the key driver for progress in this area, as part of the human capital generation project of the DST's Ten-Year National Plan for Innovation. Also create a publicly funded training programme for the production of a clinician research workforce from the top 2% of undergraduates (through student research fellowships) and 20% of postgraduates (through clinical research fellowships). A target should be set for 500 PhDs to be produced in the clinical research field over the next 10 years, while 30 Research Chairs should be earmarked for the clinical sciences. The objectives of the proposed National Clinical Scholars Programme may be achieved through:
 - a. **Expansion of the intercalated research year model of selective training of motivated undergraduates in carefully planned curricula designed to establish a life-long interest in research;**
 - b. **Re-design of the MMed research component to enhance its effectiveness in research training and competence, and to serve as the basis for MD/ PhD study;**
 - c. **Stimulating PhD degrees for professional graduates through the widening of the necessary opportunity and support mechanisms, including the use of modules and learning methodologies from BScMed honours programmes;**
 - d. **Providing a maximum of flexibility in funding possibilities and degree structures, including bursaries and fellowships that are adequate to retain promising people on their training trajectories.**
2. **Create a clinical academic career track in all disciplines in the Academic Health Complexes** under the Health Sciences Academic Development

Programme of the national Department of Health (SA Department of Health 2006). A new cadre of clinical lectureships and clinical professorships needs to be established in all clinical disciplines to rejuvenate and expand the pool of clinical research trainers and academic clinicians in general.

3. Promote **training for biostatisticians** and other supporting professions for clinical research at universities.
4. Incorporate ethics into **clinical research training and education**.
5. **Fund learnerships for graduates** in the research facilities of large multi-national and national companies.
6. Develop and support a **network of skilled mentors** who can lead the development of young clinical researchers.
7. **Create a 'National Clinical Research Coordinating Centre' at the MRC** to link and coordinate clinical research centres and clinical trials programmes at universities and research councils, and in government and industry. Such a network would foster collaborative research efforts, training programmes and research projects aimed at strengthening patient-orientated research (Rosenberg, 1999). The Centre should be given a maximum degree of operational independence while retaining overall accountability. It should seek to increase the participation of foundations, pharmaceutical companies, health insurance firms and the managed care industry in the clinical training enterprise.

REFERENCES FOR CHAPTER 7

Deo, M. G. 2008. Undergraduate medical students' research in India. *Journal of Postgraduate Medicine*. 54 (3): 176-179.

Department of Health (South Africa). 2006. *National Human Resources Plan for Health*. Available at: <http://www.health.gov.za>.

Department of Science and Technology (South Africa). 2005. *The Synthesis Paper. Paper presented at the Conference on Human Resources for Knowledge Production in South Africa, 23-24 June 2005, Cape Town.*

McManus, I. C., Richards P. and Winder B. C. 1999. *Intercalated degrees, learning styles, and career preferences: Prospective longitudinal study of UK medical students. British Medical Journal.* 319: 542-546.

Pouris, A. 2003. *South Africa's research publication record: The last ten years. South African Journal of Science.* 99: 425-428.

Price, M. (UCT) 2008. *Personal communication.*

Rosenberg, L. E. 1999. *The physician-scientist: An essential – and fragile – link in the medical research chain. The Journal of Clinical Investigation.* 103: 1621-1626.

Rosenberg, L. E. 2008. *MD/PhD programs – A call for an accounting. Journal of the American Medical Association,* 300: 1208-1209.

Smith, R. 1986. *A senseless sacrifice: The fate of intercalated degrees. British Medical Journal.* 292: 619-1620.

CHAPTER 8:

FUNDING FOR LOCAL INVESTIGATOR-INITIATED CLINICAL
RESEARCH SHOULD BE INCREASED AND BETTER
COORDINATED

In this chapter, we engage with the following questions:

1. How much should developing countries spend on medical, and specifically clinical research?
2. How much does the South African government spend on research and development, and of this, how much is spent on medical, and specifically clinical research?
3. How are funding priorities determined?
4. Through which institutions is government funding allocated?
5. What are the other sources of funding?

INTRODUCTION

The **CSIR** became the major systematic source of research funding at South African universities before handing over its role of funding medical research and managing its national research units to the newly established **Medical Research Council (MRC)** in 1969 (Brink, 1987). The successor to the CSIR in funding non-medical research, the Foundation for Research Development (FRD), functioning by statute in purely agency mode (it had no intramural research programme), was generally nervous about the dividing line between its mandate and that of the MRC, and provided very limited support to a number of basic scientists in the medical schools, as well as bursary support to a limited number of health science postgraduates. The MRC, by contrast, set up a progressively increasing intramural research programme, while supporting medical research at universities in agency mode, through joint research units and centres, self-initiated research grants to individuals, and an extensive bursary and capacity development system. It has consistently been generally recognised that the MRC, partly as a result of its 'late arrival' in the science council system and partly because of difficulties in articulating itself through the Department of Health, remains the 'Cinderella' of the annual science

vote (this limitation has turned out to be a crucial issue in later developments described below).

A good indication of the inadequacy of MRC funding levels can be obtained from our preliminary examination of the allocations in 2007/08 for **health research at universities**. Only about R12 million for operational costs was awarded to about 40 applicants/recipients for **self-initiated health-related research** throughout the country, of which only R4 million (about 30%) appeared to be destined for clinical research as defined in this report. The support for **research units and centres based** at universities was significantly greater, with the operational costs covered for about 25 such recognised enterprises, amounting to about R25 million. Of this, only about R5 million appeared to be destined for clinical research as defined in this report. The amounts for salaries at units and centres were approximately three times the operational grants, so the total investment in clinical research outside the MRC's intramural programme was about R4 million plus (R5 million \times 4 = R20 million), or just under R25 million. It is not surprising that virtually all the MRC's research units and centres based at universities obtained the majority of their funding from non-MRC sources, notably foreign foundations and government agencies, local and international drug manufacturers, and other South African funding agencies such as the NRF and the National Cancer Association of South Africa.

The MRC's intramural research programme has been extremely successful in tapping external contract funding, estimated at between R250 and R300 million per annum in 2007/08 (SA Medical Research Council Annual Report, 2008). The clinical research component appears to be quite extensive, almost entirely in the clinical trials area. Operational grants from the MRC to its own units is about R10 million, of which only about R2 million appears to be destined for clinical research. With salary components running at about five to ten times the operational grants in these intramural enterprises, the total investment in their clinical research by the MRC itself is about R10 to R20 million per annum.

The total MRC awards for clinical research in 2007/08 were thus somewhere between R35 million and R45 million. It should be noted that additional

(unquantifiable) investments were made in the form of bursaries and career development awards, but these are unlikely to exceed R5 million.

The MRC has no policy prohibiting awards for **patient-related costs** (e.g. hospital beds) or fee-for-service laboratory tests, but limits its awards to R130 000 for self-initiated research projects due to a shortage of funds. We have ascertained that very few applications currently include budgets for patient-related costs, as though the research community concerned has tacitly 'written off' the MRC as a source of funding in this domain of their budget planning. Alternatively, projects involving such expenditures are avoided. In either case, the information confirms that the funding gap left for clinical research in South Africa by the structural developments to be described below, has not been, and presently cannot be, filled by the MRC.

The **provincial governments**, during the period roughly between 1955 and 1980, contributed significantly to the promotion of clinical research through their academic hospitals, but to varying extents, depending on the nature of their partnership agreements with local universities. An important component was the pathology service rendered to academic hospitals, including tests done for clinical research purposes. In Cape Town, the partnership centred on UCT, and the Cape Provincial Administration was sufficiently successful to establish Groote Schuur Hospital as the third-most productive South African institutional contributor to top-ranked international publications indexed by the ISI in Philadelphia (see Chapter 6), after UCT itself and the University of the Witwatersrand (Clery, 1995).

A number of factors began to perturb these arrangements from the beginning of the 1980s. The rapidly declining economic situation of the late-apartheid era caused provincial health budgets to come under pressure, with the appearance for the first time of 'service-only' expenditure principles in hospital budgets. The MRC was unable to make up the shortfall; international funding sank to a very low level.

The coming of full democracy in 1994 was heralded by new health policies aimed at creating a system of **primary health care** for all, and using research

mainly to drive its attainment. Thus In 1994, South Africa formally adopted the **Essential National Health Research (ENHR)** approach in order to focus health research on issues relevant to the country. In 1996, the first ENHR congress established a list of priority health problems and identified urgent research questions. Follow-up conferences were held in 2002 and 2006 to review these priorities. HIV/AIDS, injury, TB, infectious diarrhoea and perinatal problems were identified as the top five problems (Lutge *et al.*, 2008). A formal national health research policy document, published in 2001, proposed that 2% of health expenditure should be spent on well-coordinated research (SA Department of Health, 2001).

The Foundation for Research and Development (FRD), by statutory merger with the Centre for Research Development of the **Human Sciences Research Council (HSRC)**, became the National Research Foundation (NRF) in 2000, with a broad mandate to foster and develop research capacity in South Africa. It has become by far the most powerful and significant research funding agency in the country, central to the plans of the increasingly influential **DST** to raise government investment in R&D. **The NRF has successively acted as the agent for the Innovation Fund, the Scarce Skills Fund, a system of Centres of Excellence, the South African Research Chairs Initiative, a National Equipment Plan, national large-scale facilities of various kinds, the South African Agency for Science and Technology Advancement (SAASTA), and so on (SA National Research Foundation Annual Report, 2008).** The MRC, by contrast, has had little or no share in these investments, despite significant growth in its contract income and impressive outputs in the form of publications emanating from intramural research programmes (SA Medical Research Council Annual Report, 2008).

A further issue in recent times has been the establishment of the **National Health Laboratory Service (NHLS)** as essentially a 'nationalised' form of the previous university/academic hospital pathology departments. The NHLS has not seen fit to offer clinical researchers any discounts for tests performed for research purposes, and pursues a break-even, even profit-making business policy instead, with surpluses held in reserve or kept in a 'research fund' (SA National Health Laboratory Service Annual Report, 2008).

The seriousness of the twin pandemics of HIV and TB in South Africa has focused international attention on the need for local research activity in these areas, often collaboratively with outstanding centres overseas. This has brought with it an influx of very large grants, from agencies such as the NIH and the Howard Hughes Medical Institute in the US, the Wellcome Trust in the UK, and the European Commission in the EU. Many of these grants are not sustainable, some of them are administered in a mode that amounts to externally supervised work, and no national model for the future of clinical research in South Africa can be built on them.

The aggregate and cumulative effects of the above-mentioned systemic developments in the health research sector have been very burdensome for clinical researchers, and pose a serious threat to the future of clinical research generally. They amount to a structural disinvestment and a failure so far to recognise the nature of the problem, and to design solutions that do not require reversal of sound policies in other areas of the health system.

The Department of Health policy document mentioned above emphasised the need for research to be better coordinated and regulated, and for funding resources be allocated to national health priorities based on equity and social justice (SA Department of Health, 2001). The ENHR term was coined to emphasise the importance of setting national research priorities, but two decades later much of the vision of the Commission on Health Research for Development, which included the intent to invest at least 2% of national health expenditure in research, has yet to be fulfilled. At the November 2008 Bamako Global Ministerial Forum on Research for Health, numerous critics suggested that several key African countries have done 'very little' to invest in health research since pledging to do so at a world meeting of health and science ministers in Mexico four years earlier (Report of Commission on Health Research for Development, 1990).

Globally and locally a number of factors were identified that have had a negative impact on clinical research in general. These include:

1. Lack of appropriate facilities and infrastructure to undertake patient-orientated clinical research;
2. Lack of appropriately trained clinical scientists and career structures to support them;
3. Lack of coordination of research policy and management;
4. Inadequate support from governmental health authorities;
5. Increasingly complex legal and ethical governance;
6. Inadequate funding;
7. Domination of the basic sciences over the clinical sciences.

These factors have contributed to two translational blocks, firstly the translation of basic science discoveries into clinical research, and secondly the translation of the results of clinical research into public health policy and practice.

GOVERNMENT EXPENDITURE ON RESEARCH AND DEVELOPMENT

The annual OECD-type survey by the HSRC found that South Africa spent at least R16.5 billion, or 0.92% of its GDP, on research and development (R&D) over the 2006/07 financial year, an indication that the country is progressing towards being a knowledge-based economy (SA Department of Science and Technology press release, 30 May 2008). The major source of R&D funds was from industry (49%), followed by government (33%), other sources (10%), and from abroad (7%). The intensity of R&D expenditure (measured as the percentage of GDP spent on R&D) is a good indication of the competitiveness

of a country's economy. The country with the highest R&D intensity is Sweden (3.73% of GDP in 2006). R&D expenditure in the US measured 2.62% of GDP and the average for the 27 EU member states was 1.76% in 2006. The EU has set a goal of achieving an average R&D expenditure of 3% of GDP by 2010. South Africa has set a goal of achieving R&D expenditure equivalent to 1% of GDP by 2008/09. In comparison with some other middle and lower-middle income countries, South Africa spends proportionately more on R&D than Argentina (0.49%) and Chile (0.67%), but less than China (1.42%) and the Russian Federation (1.08%) (SA Department of Science and Technology press release, 30 May 2008; <http://www.southafrica.info/about/science>).

Most South African R&D work was performed in the research field of the engineering sciences (20.9% of total R&D), followed by the natural sciences (20.3%) and the **medical and health sciences (15.1%)**. **The medical and health R&D expenditure in 2006/07 was equivalent to R2.5 billion or 0.14% of the GDP.**

The Third World Academy of Sciences recommends that 2% of the GDP of developing countries is a necessary minimum investment in indigenous science and technology development, with health research receiving 10% of that amount (<http://www.southafrica.info/about/science>).

THE PUBLIC FUNDING SITUATION FOR CLINICAL RESEARCH IN SOUTH AFRICA

There is currently no easy way to determine exactly the amount of funding which has gone towards clinical research in South Africa. The information about the **funding streams for clinical research** described previously is confined to estimates because the MRC does not itself regularly analyse its expenditures according to defined categories. Thus there is little information regarding what areas of medical and health research are funded in South Africa and accurate data on actual expenditure are not available.

Currently, 10.8% of all government expenditure is on health. The actual proportion spent on health research is very low, however. The National

Health Expenditure Review in 1991/92 estimated that only 1.1% of the total expenditure on health in South Africa was spent on research. The situation has not changed much since then, although accurate figures are not available. The 2001 Department of Health policy document on Health Research stipulates that the country's budget for health research should be raised to at least 2% of total public sector health expenditure and should be utilised to build and retain capacity and to identify, articulate and conduct priority research both internally and in international programmes. The country budget should also be utilised to promote a research culture and to strengthen research institutions. It was suggested that the DoH should increase the health research allocation from 0.5 to 1.5% of its total budget in three years. In addition, the Department of Arts, Culture, Science and Technology (DACST), DNE and the SANDF should also increase their allocations to equal 0.5% of total public health expenditure within two years.

FUNDING OF CLINICAL TRIALS BY PHARMACEUTICAL COMPANIES

The **pharmaceutical industry** estimates that clinical trials in South Africa generate approximately R2.2 billion annually; this is foreign direct investment which can make a major contribution to the ability of all South Africans to enjoy better health care and quality of life (Kirkman, 2009). Of that amount, one-half goes to **contract research organisations** for work done, while the pharmaceutical industry itself contributes R665 million. Only 1% of the total spent on clinical trials worldwide is spent in Africa, with 80% of that being spent in South Africa. This means that between 3–4% of the research budget of all pharmaceutical companies is spent on clinical trials conducted in South Africa. In 2000, however, South Africa was reported to be handling only 0.6% of the global research work, although it had a capacity to conduct 2.5% of the world's clinical research contracts (Baird and Van Niekerk, 2004).

NEW SOURCES OF FUNDING FOR CLINICAL RESEARCH IN SOUTH AFRICA

The role of government as a source of health research funding through the Science Councils, government departments and tertiary institutions has been described above. Partly in response to the falling level of support through these channels, and partly owing to other dynamics, new sources of funding for health research have increased substantially in recent years, mainly from **foreign not-for-profit sectors**, including agencies such as the US NIH, the Wellcome Trust in the UK, the Bill and Melinda Gates Foundation, the EU (the European Developing Country Trials Partnership (EDCTP)), the Howard Hughes Medical Institute, and the Aeras Global TB Vaccine Foundation. While exact details are not available, a large proportion of the funding for clinical research now being conducted in South Africa comes from these sources. As an example, **the Institute of Infectious Diseases and Molecular Medicine at the University of Cape Town, one of the leading multidisciplinary health research institutions in the country, derives approximately 60% of its funding from international private not-for-profit organisations, including the Wellcome Trust, the EDCTP, the NIH in the US and the MRC in the UK, as well as the Aeras Global TB Vaccine Foundation, while about 10% is from local non-governmental sources. South African government agencies contribute only between 20–30% of the research funding, while less than 5% of the total funding in this large enterprise is derived from the pharmaceutical industry.**

In other smaller and less well-resourced centres, the foreign and domestic pharmaceutical industry is a significant funder of clinical research, mainly in the context of drug trials. While there is no reliably published figures for pharmaceutical industry expenditure on clinical trials in the country, the Pharmaceutical Manufacturers Association estimates that it is about R900 million per annum. The South African National Clinical Trials Register lists 308 active trials by condition, without declaring their phase, whereas the NIH's US database clearly identifies 172 active industry-sponsored trials in South Africa. Another 53 trials are mainly supported by non-industry sources. Using the overall figure of 55% of R&D in South Africa being funded by business, it

is clear that the contribution of the pharmaceutical industry to South African clinical research represents at least that percentage of the spending on clinical research as well.

AGENDA SETTING FOR CLINICAL RESEARCH

The preceding analysis has indicated that the clinical research agenda in South Africa is now determined by the research needs of pharmaceutical companies and not-for-profit international consortia (as incidentally it also is in many other developing countries), simply because this is where the majority of the funding for clinical research in South Africa is now sourced.

Accessible funding flows thus set the agenda and the research priorities, instead of these being determined by the burden of disease and the health needs of South Africans in a well-coordinated and responsive manner. Speaking at the recent Bamako Ministerial summit, Dr Timothy Evans, the assistant director-general of the World Health Organisation, said that work was under way to check whether donor policies were exerting a negative effect, and they were “looking at the extent to which health priorities could be skewed by the Global Fund to fight HIV, malaria and TB”; he nevertheless cautioned that the evidence that donors were altering health priorities was mixed (<http://www.tropika.net>).

PROPOSED SOLUTIONS

1. ENHANCED PUBLIC FUNDING FOR CLINICAL RESEARCH IN SOUTH AFRICA

The public funding directed to clinical research in South Africa through the MRC is less than R50 million annually, or less than an eighth of the MRC's total annual turnover of about R400 million after current overheads of about 17.5% have been deducted. That is manifestly too little. The NRF dominates the disposition of the recent R&D investment schemes of government such as the South African Research Chairs Initiative, the DST's Centres of Excellence, the National Equipment scheme, etc., with little or no focus on clinical research,

while the MRC has no or little participation in this investment despite the general backlog associated with its late start as a science council.

It is simply not appropriate that South Africa's main residual activity in clinical research should be funded by donors and business investors, however welcome and useful this support may be.

As an example, the number of **research chairs** awarded to clinicians under the Research Chairs Initiative should be increased. Of the 72 research chairs awarded to date by the NRF, only one Tier 1 chair has gone to a clinician and two others have been awarded a Tier 2 chair (DST/NRF Research Chairs Initiative). Other chairs have been awarded in the health sciences but with a focus on the basic sciences. Representation must be made to the NRF to increase the number of chairs made available to clinicians in order to re-invigorate clinical research in South Africa. These chairs could in some way be linked to the establishment of clinical research centres. If this cannot be done, a separate scheme for the health sciences should be established. It is possible that the present **separation of reporting lines for the NRF and MRC** may have to be reconsidered if the present imbalance cannot be otherwise addressed.

2. A single national health research coordinating body

Although funding is an important concern, efficient organisation and management of research is needed to make best use of scarce resources. A major challenge is to develop a well-organised and comprehensive coordinating mechanism that will represent the diverse clinical research interests of all the relevant stakeholders in the country. Future success will depend largely on the cooperative participation of all organisations and institutions.

Key functions for such a coordinating mechanism would include:

1. Creating an enabling environment to conduct research in South Africa

There is a need to establish a clear-cut working relationship between the universities (who do the research), the provincial authorities (who provide

the clinical service to the patient or research participant) and the NHLS (who provide the laboratory services to patients or the research participant) and to ensure that these three bodies are in close communication with one another, that the roles and expectations of each party are clearly defined, and that while each party carries out its particular mandate all parties are working towards the common goal of facilitating the conduct of clinical research in South Africa. In particular the NHLS has to ensure that it meets its mandate of supporting research and that it does not 'profit' from such activities.

Additional measures to improve the operating environment for clinical researchers could include the realignment and improved coordination of the policies and operational plans of various participants, such as the DoH (now the Department of Higher Education and Training (DoHET) the DST, the DTI, the NHLS, the MRC and the provincial health departments, facilitated by the new Ministry of Coordination and Planning.

The development of a **national-level 'Joint Agreement'** between universities on the one hand, and relevant central and provincial government departments on the other, could lead systematically to the creation of a 'research platform' alongside the clinical and teaching platforms of the Academic Health Complexes as envisaged in the National Health Act of 2003.

2. Relationship building

The often tense relations that exist between scientists and clinicians, between clinician-researchers and policy-makers, and between various research providers and key stakeholders, are a barrier to ensuring that science achieves its potential impact on health care in South Africa. A major challenge is to get all the relevant stakeholders to work together to promote clinical research.

3. Advocacy and communication

Advocacy to promote clinical research in South Africa is clearly needed to ensure that it gets the appropriate share of the national research budget that it requires. In addition, advocacy to attract international donor funding and to promote North-South partnerships is essential.

Communication between the research community and the **National Treasury** needs to be focused. Researchers should be given a forum at which to present their research findings, future research goals, objectives and specific research needs that will enable them to achieve their goals and objectives. The National Treasury can then combine information obtained from this forum with information on the burden of disease in the country to make better informed decisions regarding the apportioning of government funds to national health research.

Increased communication between the various national departments (DST, DoH, DTI, DoE) will encourage interdisciplinary and innovative research at the very highest levels in the country. It will also ensure better coordination of funding of research that is mutually beneficial to all parties.

4. Ensuring that institutions provide technical and managerial support services to all their researchers

International not-for-profit consortia and other international governmental and non-governmental funding agencies are a rich source of funding for clinical research. Requests for proposals are posted on a regular basis, and it is often the case that these funding opportunities are missed due to the fact that there are no dedicated individuals within institutions whose task it is to coordinate and respond to these requests for proposals. There is an urgent need to develop capacity in the form of research administrators, grant writers and research project managers in order to harness the available funds, to assist with grant writing and to manage the utilisation of the funds in an appropriate and effective manner. Mentoring and tutoring of postgraduate and postdoctoral students in grant writing and subsequent research project administration and management is vital.

The question that arises is whether the **National Health Research Committee (NHRC)**, established by the Department of Health under the 2003 National Health Act, might be enabled to perform the central coordinating function so clearly necessary in the present situation. The NHRC has had a gestation period of almost two years, but little has been achieved in terms of its mandate

as expressed in Clause 69(3) of the National Health Act, Act 61 of 2004. The NHRC must:

- a. **determine the health research to be carried out by public health authorities;**
- b. **ensure that health research agendas and research resources focus on priority health problems;**
- c. **develop and advise the Minister on the application and implementation of an integrated national strategy for health research;**
- d. **coordinate the research activities of public health authorities.**

The NHRC has recently adopted a vision, mission and values statement:

VISION: The Vision of the National Health Research Committee is to become the key agent for priority-setting and coordination of public-sector health research in South Africa, through the provision of strategic, evidence-based and implementable advice to the Minister and Department of Health.

MISSION: The Mission of the National Health Research Committee is to combine evidence-based positions on national health priorities with enough information about research activities, capacities and contexts to generate feasible, potentially high-impact recommendations on health research to the Minister and Department of Health.

VALUES: The work of the National Health Research Committee will be done with integrity and will be evidence-based; it will be respectful but independent of the opinions and positions of its stakeholders; and it will be facilitatory in its approach to the fulfilment of its statutory mandate.

It should be evident that the NHRC, as conceived in the National Health Act of 2003, could serve as a coordinating body for the functions outlined above, provided its operational independence from government can be maximised (without affecting its overall accountability). **That it has not begun to do so four years after promulgation of the enabling Act is a great pity. If the factors that have prevented it so far from functioning according to its statutory mandate**

can be removed, the Panel would support this avenue; if not, another body with more momentum may have to be created by the stakeholders in the clinical research sector. In all cases, operational independence is a necessity.

3. Establishing a South African clinical research repository/database

Currently the DoH, the MRC and some provincial authorities are collecting and collating information on clinical trials and research (<http://www.sanctr.gov.za>; <http://www.atmregistry.org>). There is clearly a need for one central clinical research repository or database that will collect and collate data on all aspects of clinical research (i.e. funding, outputs, capacity development and career development opportunities) in South Africa. This will assist policy-makers to make informed decisions regarding the current and future state of clinical research in South Africa, in particular to determine:

- a. The current level of clinical research funding in South Africa;
- b. The sources of clinical research funding in South Africa;
- c. The relationships between available funds for clinical research and research agenda/priority setting in South Africa.

4. Creating specific clinical research facilities in health facilities

There is a real need for **regional clinical research centres or hubs** to be established, with sufficient clinical and preclinical expertise and facilities to work at a high level. Such facilities should be supported and funded through specific grants from central government (via the DoH or the MRC). Support for these facilities could also be obtained from the pharmaceutical industry and from other donors. Some of these facilities should be developed into **large-scale research institutes**, with a critical mass of principal investigators, postdoctoral fellows, graduate students and research assistants.

Research in primary care or community settings also needs to be developed to facilitate large-scale trials, cohort studies and diagnostic studies. These centres must have close contact with academic centres.

Investments in such facilities will go a long way towards strengthening academic medicine and clinical research that will ultimately benefit the community at large.

FINDINGS

1. Two per cent of the GDP of developing countries is a necessary minimum investment in indigenous science and technology development, with health research receiving at least 20% of that amount.
 - a. **South Africa is spending more on R&D than before, but this is still under 1% of GDP; the largest part is spent on the engineering and technological sciences and on the natural sciences (40% of total R&D spend, about 20% each), while expenditure on the health sciences is 15% of the total (about 0.15% of GDP). The government spends a large amount on services in the public health sector (about 10% of all government expenditure), but much too little of this money is spent on health research, which is also poorly coordinated and inadequately documented;**
 - b. **Clinical trial expenditure by industry is not included in this figure. Most of the current funding for health research comes from donors outside the country and from the pharmaceutical industry. More than half of the total expenditure on clinical research is by the private (business) sector.**
2. The key narrative of clinical research funding over the last two decades is:
 - a. **Cumulative disinvestment resulting from an abrupt withdrawal from this sector of the health departments of provincial governments;**
 - b. **The absence of discounts for research tests from the business model of the NHLS;**
 - c. **Chronic under-funding of the MRC despite its explicit mandate for supporting and developing medical and clinical research capacity in the country;**

- d. The lack of funding streams to universities that might in principle have been applied to meet the overall shortfall in support.**
- 3. Most of the external donor funding is directed at the serious local HIV and TB pandemics, while the pharmaceutical investment is directed predominantly at the profitable areas of chronic diseases of lifestyle, mental illness and allergy.
- 4. Local and international clinical conference activity has accordingly begun to reflect the agendas of industry and donors rather than the health priorities of the country, as has the pattern of publication outputs.

RECOMMENDATIONS

- 1. Encourage the Department of Health (DoH) to enable the National Health Research Committee (NHRC), or a similar body, independently to perform the key functions of:
 - a. Creating an enabling environment to conduct research in South Africa;**
 - b. Building better relationships between scientists and clinicians, between clinician-researchers and policy-making, etc;**
 - c. Promoting clinical research in South Africa;**
 - d. Communicating between the research community, the National Treasury and the various national departments;**
 - e. Ensuring that institutions provide technical and managerial support services to all their researchers;**
 - f. Improving regulatory procedures.**
- 2. Enable more effective tracking and monitoring of funding streams for clinical research.

3. Substantially increase public funding of clinical research, applied in such a way that national health priorities are more effectively addressed than is currently the case. The DoH should allocate 2% of its allocation to health research.
4. Realign and increase coordination of the policies and operational plans of various participants such as the DoH, the DoE, the DST, the DTI, the NHLS, the MRC and the provincial health departments, facilitated by the new Ministry of Coordination and Planning. Specifically, the lagging position of health research (MRC) in respect of national stimulation programmes and interventions such as the Research Chairs Initiative, the Centres of Excellence programme and the major equipment programme, must be addressed.
5. Develop a National Joint Agreement between universities and the Departments of Health and Education, which should provide systematically for a 'research platform' alongside the clinical and teaching platforms of the Academic Health Complexes as envisaged in the National Health Act of 2003.
6. Create regional clinical research centres/hubs with clinical and preclinical expertise and facilities.

REFERENCES FOR CHAPTER 8

Baird, D. and van Niekerk, D. 2004. *The Regulation of Clinical Trials in South Africa*. *Quality Assurance Journal*. 8: 33-36.

Brink, A. J. 1987. *Medical research: From pastime to profession*. In: Brink, A. J. *South African Medical Research: Twenty Years of Growth*. Pinetown: Owen Burgess.

Clerly, D. 1995. *Elite science in a poor country*. *Science*. 268: 1282-1286.

Department of Health (South Africa). 2001. *Health Research Policy in South Africa*.

Department of Science and Technology (South Africa). Press release, 30 May 2008. Available at: <http://www.dst.gov.za/media-room/press-releases-1/sa2019s-public-r-d-spending-on-target>.

DST/NRF Research Chairs Initiative. Available at: <http://www.nrf.ac.za/sarchi/index.stm>.

HIV/AIDS, Tuberculosis and Malaria (ATM) Clinical Trials Registry. Available at: <http://www.atmregistry.org/> Kirkman, M. 2009. Unpublished data (ibid).

Lutge, E., Friedman, I. and Mbatha T. 2008. A review of health research in South Africa from 1994 to 2007. Health Systems Trust 2008. Available at: <http://www.doh.gov.za/docs/reports/2001/enhr/chapter1a.pdf>.

National Health Act, Act. 61 of 2004. Available at: <http://www.doh.gov.za/docs/legislation-f.html>.

Report of the Commission on Health Research for Development 1990. Available at: <http://www.cohred.org/main>.

South African Information. Available at: <http://www.southafrica.info/about/science/md-180908.htm> South African Medical Research Council Annual Report 2008. Available at: http://mrc.ac.za/annualreport/annual2007_8.html.

South African National Clinical Trials Register (SANCTR). Available at: <http://www.sanctr.gov.za/>.

South African National Health Laboratory Service Annual Report 2008. Available at: http://www.nhls.ac.za/pub_annual.html.

South African National Research Foundation Annual Report 2008. Available at: http://www.nrf.ac.za/publications/annrep/08/pdfs/annualreport07_08/pdf.

Tropical Diseases Research to Foster Innovation and Knowledge Application (TropIKA). Available at: http://www.tropika.net/svc/news/20081117/Chinnock20081117_Bamako_News_Opening_Speakers.

CHAPTER 9:

THE ROLE OF INDUSTRY AND THE MEDICAL REGULATORY
AUTHORITY IN PROMOTING CLINICAL RESEARCH

In this chapter, we engage with the following questions:

1. What are the existing institutional arrangements for specific investments in clinical research in South Africa?
2. What kinds of interaction do we need between government, parastatal institutions, academia and industry to revitalise clinical research?

INTRODUCTION

There are still many diseases for which there is no cure or current treatment is inadequate. In addition, there are new diseases and conditions which have developed over the past few years such as HIV/AIDS, avian influenza, multidrug-resistant TB, extensively drug-resistant TB and others. Although knowledge of these diseases is growing rapidly, some of them are very complex, and the need for continuing research into disease mechanisms and treatments, including new medicines, is immense. Thus the demand for highly trained and skilled research scientists and adequate financial resources dedicated to research is continually growing.

The **global clinical trials business** was worth an estimated US\$50bn in 2008, with an annual growth of rate of 10% (<http://www.pharma.org>). Increased emphasis has been placed on the cost-effectiveness of pharmaceutical R&D, as well as on increased productivity to maintain the high output of recent years. Consequently, the pharmaceutical industry has witnessed a rapid expansion of outsourced clinical services in both the West and in developing nations, most notably India and China, as well as countries in Eastern Europe. A report in January 2009 by the Tufts Centre for the Study of Drug Development indicates that the percentage of FDA researchers outside the US has increased significantly over the past 10 years, while the proportion of those based in the US has declined significantly, i.e. to only about 54% of the FDA-regulated chief scientists who conducted clinical trials in 2008.

Pharmaceutical companies around the world are seeking **alternative clinical trial sites** due to shortages of both subjects and investigators in the traditional

regions (US and Western Europe) as well as the cost savings which can be achieved by locating clinical trials in developing countries such as eastern Europe, India and China, the latter being two of the world's most populous countries and once considered difficult markets to enter. Both countries have taken significant strides as emerging markets in drug development. It is no coincidence that over the last decade or more of economic liberalisation, and years of unprecedented growth, India and China are becoming preferred destinations among emerging countries to which multinational pharmaceutical and biotechnology corporations as well as NGOs are outsourcing many clinical trials.

A recent study published in the *New England Journal of Medicine* indicates that in November 2007 about one third of Phase III trials and studies of industry-sponsored trials conducted by the 20 largest US-based pharmaceutical companies were performed outside the US, mostly in countries in Eastern Europe and the Russian Federation. Some concerns have been expressed about trading the lower costs of drug development for medicines that may be less safe and less effective. There has been widespread adoption of the ICH-GCP Guidelines, however, which may provide some safeguards for studies in such countries (Glickman *et al.*, 2009), even though some critics have taken issue with the methodology of the Duke University study (Getz *et al.*, 2009). The FDA is also training regulators in some countries to ensure a robust research and regulatory framework that will protect trial participants and ensure that clinical research is conducted to the highest scientific standards.

South Africa already participates extensively in clinical research. The issue to be addressed is how all role-players (government, parastatal research and academic institutes and industry) can collaborate to make South Africa an attractive destination for clinical research by creating a more favourable and enabling environment.

Despite all that has been said in previous chapters about the problems besetting clinical research in the country, South Africa seen from the outside still has an impressive array of clinical resources, a large and diverse population of treatment-naïve subjects to participate in clinical trials, a large diversity of

disease conditions, and well-trained health professionals, modern medical facilities and extensive infrastructure.

In recognition of the fact that the South African regulatory system, the Ethics Committees, the standard of training of health care professionals and the available infrastructure are all appropriate for conducting clinical trials to international standards, reports of clinical studies conducted in South Africa are frequently used elsewhere to obtain marketing approval (registration) for medicines – the trials concerned are readily accepted by the medicines regulatory authorities in most developed countries.

While pharmaceutical and biotechnological companies are traditionally involved in the development of new medicines, including the sponsorship of clinical trials, NGOs worldwide are increasingly responsible for conducting clinical trials for new treatments to address the diseases of the developing world. In addition, the pharmaceutical and biotechnology industries are increasingly delegating the responsibility of clinical trials to contract research organisations (CROs); this trend is also evident in South Africa where a recent survey by the South African Clinical Research Association (SACRA) has revealed that the ratio of R&D spend between pharmaceutical houses and CROs is already 27:73 (available by e-mail from SACRA 2009 at Maureen@piasa.co.za).

In terms of the **National Industrial Policy Framework (NIPF)** and the **Industrial Policy Action Plan (IPAP)**, the South African Government has identified the pharmaceutical industry as a 'priority' industry to fuel economic growth in order to meet the growth objectives of **ASGISA (Accelerated Shared Growth Initiative of South Africa)**. To ensure the success of these initiatives, it is imperative that there is coordination and communication between different government departments so that all work together towards achieving the stated goal of sustained and positive economic growth in South Africa (PIASA, 2009).

To quote the NIPF, "industrial policy is not the domain of a single government department but requires intensive coordination across a range of government

departments. It can only be implemented successfully if there is alignment with four associated and supporting sets of policies: First, a stable and supportive macro-economic and regulatory environment; second, appropriate skills development and education systems which are increasingly integrated with the needs of the industrial economy; third, sufficient, reliable and competitively priced traditional and modern infrastructure; and fourth, adequate support for various forms of technological effort within the economy" (National Industrial Policy Framework; PIASA, 2009).'

THE CRUCIAL ROLE OF THE 'MEDICINES REGULATORY AUTHORITY' IN SOUTH AFRICA

The current South African Medicines Regulatory Authority (MRA) is the **Medicines Control Council (MCC)**, established in terms of the Medicines and Related Substances Control Act, Act 101 of 1965, which has been amended several times, most recently in 2008 (Medicines and Related Substances Control Amendment Bill, No. 44D of 2008). Due to the development of a huge backlog in approvals of both new products for registration, change to existing registered product dossiers, and unacceptable delays in clinical trials approvals, the Minister of Health in 2006 appointed a Ministerial Task Team (MTT) to review the current structure and functions of the MCC and to recommend the most appropriate medicines regulatory structure for South Africa for the future. The MTT was chaired by Prof. R Green Thompson and had two independent experts with wide international experience. The MTT report (Ministerial Task Team Report, 2008) was presented to the Minister of Health early in 2008.

Some of the recommendations of the MTT were incorporated into the latest amendments to legislation. The amendments will abolish the current MCC and instead establish a **South African Health Products Regulatory Authority, SAHRA**, which will control all health products including evidence-based medicine and complementary medicines, medical devices and foods or cosmetics that contain scheduled substances. All medicines and other health products will have to be **registered** before they can be sold. Registration of a medicine

will be based on expert review of the evidence that the medicine meets international standards for safety, quality and efficacy, which evidence must be provided to the Authority by the applicant. The review is conducted by a panel of experts selected for their integrity, as well as their scientific expertise, independence and insight. All medicines approved for registration must be evidence and clinical practice-based. Since registration (or marketing approval) is the last step in the chain of development of a new medicine, it is crucial that the regulatory process be efficient and that approval, if justified, be granted without undue bureaucratic delays.

Clinical trials to establish the safety and efficacy of new medicines are conducted in countries around the world. Many of the Phase III studies are multi-centre studies conducted in different centres or different countries according to the same protocol and running in parallel. Some of these studies are conducted in South Africa and there is every reason to believe that this could be increased by 250% to 500% (2½ to 5 times) (Beare Pharmaceutical Industry Report, 2001).

It is generally agreed that the current **timelines for approval of clinical trials** by the MCC are simply too long (up to six months) and these delays are impacting on the completion dates for the dossiers needed for submissions for marketing approval in all countries in which a submitting company operates. Such delays hold up marketing approval (registration in South Africa) and thus entry to the market, shortening the patent life for new inventions which are the lifeblood of innovative pharmaceutical companies. Over the past few years, many clinical trials which could have been successfully conducted in South Africa have been moved to other countries where the approval period was considered more efficient and the trials could be completed within an acceptable time frame.

In many countries, dialogue between the applicants for approval of registration or for approval of a clinical trial and the reviewers for the relevant MRA has become a standard feature of the approval process. This process clarifies the requirements and data submitted, facilitates understanding and often saves months of correspondence. While this is permitted in South Africa, in practice

it is usually extremely difficult for applicants to meet with reviewers or to clarify information needed for the approval process.

A NEW APPROVAL PROCEDURE RECOMMENDED FOR SOUTH AFRICA?

Most role-players involved in conducting clinical trials in South Africa, i.e. academic and research institutions, the pharmaceutical industry, and all independent Contract Research Organisations (CROs) involved in conducting clinical trials under contract to a sponsor either in South Africa or abroad, have recommended that the procedure for approval of clinical trials in South Africa be amended in order to address the current delays being experienced.

Three organisations – the African Clinical Research Organisation of South Africa (ACROSA), the South African Association of Pharmaceutical Physicians (SAAPP) and the South African Clinical Research Association (SACRA) – representing professionals involved in conducting and monitoring clinical trials together conducted a study of the procedures in South Africa and compared these with those followed by MRAs in other countries.

From this study it appears that a process applicable in several other countries could be adopted in South Africa without compromising patient safety and with full regard to ethical considerations.

1. Ethics Committee approval

In Australia, ethics committees approve or reject clinical trials, and **notify** the relevant regulatory authority that the clinical trial has been approved by the ethics committee. This is similar to the system used in Ghana and Uganda, the only other African countries represented in the study, where the regulatory authorities also do not conduct routine reviews of clinical trial applications.

This approach is supported by the multinational members of the Pharmaceutical Industry Association of South Africa (PIASA) for future approvals, and was recommended to the MTT mentioned above. It is clear, however, that the

delegated pathway will only be appropriate in South Africa when the National Health Research Ethics Council (NHREC) has developed the criteria for accreditation of those research ethics committees which meet internationally acceptable standards. Thus the clinical trials industry at present accepts that the MCC reviews ensure the protection of vulnerable populations in South Africa by also ensuring protocols and that the conduct of clinical trials meets ethical criteria.

2. MRA approval to conduct a clinical trial

The procedure followed in Austria, Canada, Ireland, the Netherlands and the US is that an application to conduct a clinical trial is submitted to the MRA and the company or institution can proceed with the trial if a no objection letter (NOL) is received from the MRA within a specified time frame, e.g. objections to a clinical trial application must be forwarded to the applicant within a period of 30 calendar days from the date of submission of the trial application to the MCC, failing which a no objection letter is sent to the applicant indicating that the study may proceed. The average time to approval in the countries listed above is two months. If queries or objections are raised, an additional 25 calendar days are allocated for the review of responses; if no objections are raised within the specified time period, the trial is allowed to proceed.

A longer period, e.g. 25 additional calendar days, can be used for applications involving studies on innovative products or gene therapies to provide a longer review period.

This approach is illustrated in the diagram below:

Recommended procedure for clinical trial approvals		
CTA Submission	EC application	
Can proceed within specific time frame, OR if company receives no objection letter	EC approval	
<ul style="list-style-type: none"> In many countries, ethics committee approval is required before regulatory authority approval is granted. However, it is recommended that in South Africa applications be made simultaneously to the ethics committee and the MRA but that the MRA's NOL letter not be sent until EC approval is received. 		
Country (Months to approval)	Austria (1.5) Canada (2) Ireland (2) The Netherlands (2) US (2) Average (2)	

(Source: ACROSA, SAAPP and SACRA, 2006)

This system is used in five of the 51 countries represented in the above study and appears to be an efficient system for getting trials approved (ACROSA, SAAPP and SACRA, 2006).

In some countries the regulatory authority is required to stop or delay studies rather than approve them. This system works well in all countries currently using it, as the approval process is efficient. Within the South African MCC, the clinical trials department is responsible for the timely review of applications by the **Clinical Trials Committee**, which is currently a highly problematic process. While it has been suggested that an alert system might be implemented to ensure that the Registrar of the MCC is notified every time a response letter is not sent within the specified 30-day period, or a reward or penalty system implemented to motivate the clinical trials department to meet their deadlines, these measures need to be carefully considered. A potential flaw in this system is the lodging of non-specific objections. This practice would have to be monitored and strongly discouraged by internal Quality Management Systems within the MCC. Regulations should stipulate that a trial may only be delayed by a specific scientific concern relating to the safety or quality of the investigational product or any potential hazard to the participants.

The present requirement of both a review by the Clinical Trials Committee (CTC) and ratification by the Council (MCC) appears to be both unnecessary and a waste of a very scarce resource (the clinical expertise of the CTC members). The CTC should be empowered to issue a NOL without additional ratification from the MCC, as this second step serves no useful purpose and currently delays an already lengthy process. In any case, the dual process should be eliminated once the new authority, i.e. SAHRA, is established. The current parallel submission and review of the MCC and ethics committee applications should be maintained, however. A new system along these lines would remove one of the major obstacles to preventing South Africa from attracting many clinical trials.

3. The role of industry and its limits

Undergraduate training

Several multinational pharmaceutical companies offer bursaries for the training of undergraduates in the health sciences. The R&D-based multinational pharmaceutical companies in fact awarded bursaries sufficient to put 147 professionals through the tertiary educational system in 2006. Some of the bursaries channel the funding through universities or professional societies such as the Foundation for Pharmaceutical Education (managed by a Board of Governors under the auspices of the Pharmaceutical Society of South Africa).

Postgraduate training

Funding is offered for fellowships or master's degrees in specific areas of research by several companies, and it is likely that this could be considerably expanded if certainty returns to the market, i.e. if a number of government and industry initiatives relating to issues such as pricing regulations, Black Economic Empowerment (BEE) and the Health Charter are resolved.

Training in current Good Clinical Practice (cGCP)

The pool of potential experienced clinical investigators is relatively small. Attempts have been made by the medical research faculties of some universities as well as various pharmaceutical companies and most recently by PIASA, a trade association representing pharmaceutical manufacturers, to build additional capacity and a larger skills base by offering subsidised training in cGCP for both potential investigators and research assistants, particularly those from previously disadvantaged backgrounds (Ms M. Kirkman, Personal Communication).

Funding of research institutions

Some pharmaceutical companies have been involved in the sponsorship of research institutes, such as the Lung Institute at UCT funded by Boehringer Ingelheim.

Corporate social responsibility programmes

Many of these programmes have been running for many years, and the Corporate Social Responsibility (CSR) activities of ten major pharmaceutical companies have been valued at approximately R1.5 billion (Deloitte Report, 2007).

Recommendations for consideration

It is possible that the above programmes or similar new programmes may be expanded further, including more specific training programmes, as part of the commitments to be made by multinational companies in terms of the Health Charter. Failing determination of a specific Health Charter, industries are expected to conform to the requirements of the Broad-Based Black Economic Empowerment (BBBEE) Act. This will involve commitments to participate in capacity building, skills development, enterprise development and corporate social responsibility projects. Negotiations with both the DTI (the custodian of BEE implementation) and the DoH will be needed to ensure the most favourable outcome for the country.

An exciting possibility to be investigated is a form of **learnership** for graduates or those with postgraduate qualifications to be placed in the research facilities of large multinational companies where specific areas of learning could include the research methodology involved in the investigation of new molecules, and all the different stages of drug development including the clinical phases. This would require a long-term commitment (20 to 25 years) where the benefits would not be experienced for at least 10 to 15 years. This may be considered in terms of the proposals for the Health Charter for the private health sector concerning a commitment by the pharmaceutical industry to building capacity in the country and developing those specific scientific skills which are in short supply.

LIMITS OF INDUSTRY

South African subsidiaries of the research-based multinational pharmaceutical industry

Most innovative pharmaceutical companies have a central R&D division generally situated at or near the head office of the company. Nearly all research scientists employed by the company are thus usually in one research facility. In some cases there is also a contract or agreement with a research institution or university where the faculty staff will be engaged with the company R&D staff in a partnership to discover and develop new medicines. In the US, the NIH has conducted early-stage research into a number of molecules which have then been the subject of an agreement with a pharmaceutical company to develop the medicine into a product which can be marketed.

This central control of all research is often due to the very high costs of rational drug development, including the required investigations into animal pharmacology and toxicology, human pharmacology and pharmacokinetics, leading to clinical trials. The costs of developing a new chemical entity which can be marketed are today estimated to average US\$1 billion. The company assumes the risk of development, and benefits from a limited period of patent protection, while it shares or pays royalties to the original developer of the molecule (GlaxoSmithKline *et al.*, 2008).

The ability of South African subsidiaries of multinational pharmaceutical companies to determine which clinical studies will be conducted in South Africa is severely limited, since all decisions are made at the central R&D division at headquarters. As mentioned above, South African subsidiaries must compete against subsidiaries of the same company in other countries in order to attract clinical studies to South Africa.

Some input into the selection of clinical trials suitable for South Africa will sometimes be considered, as will recommendations for studies into therapeutic areas of special interest to South Africa. If the study is specific for South Africa, the protocol will be discussed with the clinical department of the South African subsidiary and with the local principal investigator. Very few changes can be made to the protocol for multi-centre studies when these are being conducted in several different countries.

Local South African industry and research

Most local companies are involved in the development of different formulations and dosage forms for generic medicines. Bioequivalence studies must be conducted on most of the solid oral dosage forms to ensure bioequivalence with the originator medicine registered in this country and for which the company will have supplied the required clinical evidence in order to obtain approval of registration by the Medicines Regulatory Authority (Scholtz *et al.*, 2005).

Key Issues

1. Medicines regulatory process for approval of clinical trials

Approval of clinical trials should be left to properly constituted and accredited ethics committees as is done in Australia, which approve or reject clinical trials, and the regulatory authority is only **notified** of the clinical trial approved by the ethics committee. This is similar to the system also used in Ghana and Uganda.

Alternatively the South African MRA should amend its current procedures and adopt one already tried and tested in several other countries, viz. Austria, Canada, Ireland, the Netherlands and the US, where the company or institution proceeds with the trial if a no objection letter is received from the MRA within a specified time after an application to conduct a clinical trial has been submitted. The average time to approval should be less than two months.

Many more clinical trials could be conducted in South Africa even under the present regimen if there were a general recognition of South Africa as a 'centre of excellence' for the conduct of such studies. This would require that:

- a. the MRA and industry agree on a reasonable time to approval for clinical trial applications, e.g. a reduction of approval time to no longer than eight weeks;**
- b. efficient processing be done of all applications with clearly understood requirements;**
- c. the National Ethics Research Council complete its process for accrediting ethics committees, and these were able to process applications in a time periods of less than six weeks.**

2. Staffing levels in public sector hospitals

The lack of adequate staffing levels of doctors and nurses in public hospitals is a severely limiting factor attracting more clinical studies to this critically important sector. The DoH and the provincial health departments will need to ensure the recruitment and retention of adequate numbers of medical practitioners, nurses and support staff in public sector hospitals to ensure that it will be possible to conduct more clinical trials in public hospitals.

3. Role of industry

It is possible that current schemes for bursaries, grants and training opportunities could be significantly expanded, particularly with respect to trials-specific

training programmes, as part of the commitments to be made by multinational companies in terms of the Health Charter.

Forms of **learnership** for graduates or postgraduates could be developed in the research facilities of large multinational companies where specific areas of learning could include the research methodology involved in the investigation of new molecules, and in all the different stages of drug development, including all preclinical and clinical phases. This would require a long-term commitment (20 to 25 years) where the benefits would not be experienced for at least 10 to 15 years.

4. Partnerships

Local subsidiaries of multinational companies could possibly increase the involvement of global alliances to address diseases prevalent in the region. Given the existing infrastructure, the strong regulatory oversight, the international recognition of the competence of the training of health professionals in clinical research, our diverse population and disease conditions, South Africa could become an attractive partner for outsourcing of clinical trials with the potential for success similar to that of India.

5. International competitiveness

5.1 Dialogue

The recommendation for regular dialogue between the SAHRA and industry will have a beneficial effect and help to resolve many outstanding issues, which could facilitate speedier approval of clinical trials and thus assist in making South Africa more competitive.

5.2 Alternative procedures

The implementation of the amendments to the legislation including the restructuring of the MRA, will be an ideal time to introduce one of the alternative procedures for approval of clinical trials as recommended in Section 1 above. This would place South Africa on a par with several developed countries

with regard to competing for a share of global clinical trials and increase its attractiveness as a venue for such studies.

5.3 Agreed time lines for approval

Reasonable target time lines for approval after submission of applications to conduct clinical trials are to be set and agreed from time to time with industry (PIASA submissions 2006-2007).

5.4 Other recommendations for measures to improve the registration process and times

There could be an agreement to recognise prior approval of trial proposals in selected countries to facilitate faster review processes, since local reviewers would be able to rely on a thorough evaluation by reviewers in these other countries.

Where application is made for the registration of an identical product under another trade name for strategic marketing reasons, only one 'master dossier' could be submitted and reviewed. This would prevent the wastage of skilled human resources through duplication of work.

5.5 Link-up with intellectual property issues and legislation/regulations

An extremely important aspect of regulation concerns the measures recently put in place by the South African Government for protection of intellectual property generated with public funding, notably the **Intellectual Property Rights from Publicly Financed Research and Development, Act 51 of 2008**, and the **draft Regulations** under the Act currently being circulated for public comment. The Act seeks to "provide for more effective utilisation of intellectual property emanating from publicly financed research and development; to establish the National Intellectual Property Management Office and the Intellectual Property Fund; to provide for the establishment of offices of technology transfer at institutions; and to provide for matters connected therewith."

The implementation of the Intellectual Property Rights Act and the finalisation of the Regulations must clearly engage fully with the important area of clinical research and trials, so that the benefits to society and the economics of patents and their commercialisation are maximised. The necessary interface between the regulatory regimens of both the ethical and intellectual property systems must be both efficient and effective. It is important also that the one system should not become an impediment to the other.

CONCLUSIONS

South Africa should again become internationally recognised as a **centre of excellence** for clinical research, including for clinical trials. Appropriate intellectual property protection and development is a necessary and important element of the infrastructure of such a platform.

This requires all role-players in government, i.e. the DoH, including the Directorate responsible for health research, and particularly the Medicines Regulatory Authority, the DST, the dti, the MRC, as well as research institutes and other academic centres and both the pharmaceutical industry and the clinical research industry to work together to achieve this. This would greatly improve the climate for investment in South Africa and result in better access to the most advanced medicines and treatments for the public in South Africa, as the innovative medicines of today become the generic medicines of tomorrow. Investment in clinical studies conducted in South Africa is likely to increase the knowledge and understanding of the South African market and regulatory systems, thus attracting investments in other areas as well.

FINDINGS

1. South Africa could be recognised as a centre of excellence for clinical trials which could attract more investment in trials. This would ensure retention of skilled scientists and retention of the ability of medical research facilities at universities or research institutions to continue to do basic and novel medicine research and attract foreign direct investment to the benefit of the South African economy.

2. The present Medicines Control Council's Clinical Trials Committee performs a review function on all clinical trials. This process, which has improved recently prior to its legislated change into a Regulatory Authority (RA), still experiences problems, such as approval delays, variation in reviewer quality and inadequate supervision of trials.

RECOMMENDATIONS

1. The new Medicines Regulatory Authority (MRA) should rigorously meet its statutory requirements to ensure that any medicines used in the country are safe and effective.
2. The MRA should rely on sound ethics review.
3. An increase in the number of clinical trials conducted in South Africa (with recognition of South Africa as a centre of excellence for conducting such studies) would require:
 - a. **agreement on a reasonable time-to-approval for clinical trial applications (e.g. a reduction of approval time to no longer than eight weeks);**
 - b. **efficient processing of all applications with clearly understood requirements;**
 - c. **regular dialogue between the SAHRA and all role-players.**
4. The regulatory process for approval of clinical trials could be expedited in the following ways:
 - a. **After auditing, standardisation and accreditation of RECs by the NHREC, a system could be envisaged in which RECs approve or reject clinical trials and then notify the RA of the clinical trial; the RA would thus avoid conducting routine reviews of clinical trial applications; or**

- b. Once an application to conduct a clinical trial is submitted to the MRA, the company or institution could proceed with the trial if a no objection letter was received from the RA within a specified timeframe;**
 - c. Where application is made for the registration of an identical product under another trade name for strategic marketing reasons, only one 'master dossier' could be submitted and reviewed;**
 - d. There could be recognition of prior approval in selected countries;**
 - e. The RA should rely on the local REC for ongoing audits of studies they have approved.**
5. The implementation of the Intellectual Property Rights Act of 2008 needs to be carefully and deliberately aligned with the ethical regulatory aspects of the system.

REFERENCES FOR CHAPTER 9

ACROSA, SAAPP and SACRA. 2006. Recommendations for Improving the Clinical Trial Review Process in South Africa. 11 December 2006.

Department of Trade and Industry (South Africa). 2001. Beare Pharmaceutical Industry Report 2001 – SA; see also Beare and Laing, *Scoping study for the DTI 2001*.

Deloitte. 2007. Deloitte Report on the Economic and Socio-economic Benefits of the R&D-based Multinational Pharmaceuticals on the SA economy.

Getz, K. et al. 2009. Tufts Centre for the Study of Drug Development. Report.

GlaxoSmithKline (GSK) 2008. Harvard University, Astra Zeneca and Columbia University. *Scrip World Pharmaceutical News*, October.

Glickman, S. W., McHutchison, J. G., Peterson, E. D., Cairns, C. B., Harrington, R. A., Califf, R. M. and Schulman, K. A. 2009. Duke University Clinical Research Institute: Ethical and scientific implications of the globalization of clinical research. *New England Journal of Medicine*. 360: 816-823.

Ms M Kirkman (Executive Consultant for Pharmaceutical Industry Association of South Africa), Personal communication.

Industrial Policy Action Plan [IPAP]. Available at: <http://www.dti.gov.za>.

Medicines and Related Substances Control Act, Act 101 of 1965 as amended. Available at: <http://www.doh.gov.za>.

Medicines and Related Substances Control Amendment Bill No. 44D of 2008. Available at: <http://www.doh.gov.za>.

Ministerial Task Team Report [MTT]. 2008. Available at: <http://www.mccza.com>.

National Industrial Policy Framework [NIPF]. Available at: <http://www.dti.gov.za>.

Pharmaceutical Industry Association of South Africa (PIASA). 2007. Submissions to the MTT from October 2006– January 2007.

Pharmaceutical Industry Association of South Africa (PIASA). 2009. Submission to the South African Revenue Services (SARS) on clinical trials in South Africa.

Pharmaceutical Research Manufacturers of America. Available at: <http://www.phrma.org>.

CHAPTER 10:

MODELS FOR DEVELOPING AND PROMOTING CLINICAL
RESEARCH ADOPTED ELSEWHERE IN THE WORLD

In this chapter, we engage with the following question:

What kinds of interventions have been used elsewhere in the world successfully to address the kinds of challenges South African clinical research is facing?

INTRODUCTION

Although health research is acknowledged as indispensable for improving health, promoting equity and stimulating development, there is a great need for more discussion on how **developing countries** – especially those in sub-Saharan Africa – can build up their fragile health systems and develop their own capacity to conduct health research (Whitworth *et al.*, 2008).

In his paper entitled '**Research Capacity Strengthening in the South**', Thomas Nchida of the Global Forum for Health Research at the WHO observed that in the South, "(clinical) research capacity remains one of world's unmet challenges (while) nations in the South bear the greatest burden of the world's health problems." Funding for clinical research in these countries is scant to virtually non-existent; there is a lack of appropriate research infrastructure, and a scarcity in both the numbers and quality of trained researchers. Clinical research receives little or no recognition from the state, and there is "often a complete rupture between the scientist and the policy-makers in the ministries (of health) in the South"; health officials are often indifferent or even hostile to research-based health care solutions. Scientists in the South suffer from "demotivation, isolation from peers, poor access to the literature, (and) very low salaries" (Nchida, 2002).

It must be said, however, that concerns about the threats to the development, promotion, conduct and translation of clinical research are not the exclusive domain of developing countries. While biomedical research in the North is generously endowed in material and human terms compared to the South, clinical research there is not without problems of its own. For example, a report in the *Lancet* observes that "Health and legislative systems in Europe fragment clinical research and dampen its competitiveness, reducing the capacity to

enrol patients in clinical studies, increasing the costs of clinical research, and hampering scientific productivity" (Nchida, 2002). Cross-border research in the EU is hampered by language diversity and lack of regulatory harmony among member states in such areas as ethical review policies, research regulations and legislation. There are thus many challenges in the North with which the South can identify. These also include the need continually to strengthen and retain research capacity in terms of skilled clinical researchers, to continually increase funding levels to keep up with technological and other developments, and to strengthen translational research. Many developed countries are continually developing and implementing measures to deal with these challenges, and this chapter looks at some of the strategies that may serve as models to address impediments to clinical research in the South.

First, it must be noted that the problems of the shortfalls in facilities and infrastructure, public engagement, funding and the supply of clinician scientists for clinical research in South Africa are fully addressed elsewhere in this report. Similarly, some **specific models from elsewhere in the world** are covered in earlier chapters in their context. The purpose of this chapter is to chart some broader initiatives from other countries to meet common challenges.

Translational research

In 2003, **Britain's Academy of Medical Sciences**, made up of over 700 of the UK's leading medical scientists from hospitals, academia, industry and public service, published a report entitled *Strengthening Medical Research* in which they identified "a substantial gulf between basic discoveries and converting such discoveries into innovations that directly benefit patients or prevent disease." It attributed this disjuncture to a dramatic worldwide shift of focus in scientific inquiry from clinical research to laboratory investigation at a cellular and molecular level, following the emergence in the 1970s of the tools and techniques of molecular biology and the capacity to manipulate and transfer genes between populations. The report suggests that "this translational gap can only be bridged through the successful application of clinical research, testing and evaluating new concepts and interventions at

the bedside and in carefully managed clinical trials" (Academy of Medical Sciences, 2003). This concern is shared by researchers in the US, who have noted that "growing barriers between clinical and basic research, along with the ever-increasing complexities involved in conducting clinical research, are making it more difficult to translate new knowledge to the clinic – and back again to the bench. These challenges are limiting professional interest in the field and hampering the clinical research enterprise at a time when it should be expanding" (<http://www.nihroadmap.nih.gov>).

The British Academy of Medical Sciences attribute the abovementioned gulf to the relative retrogression of clinical research which it attributes to five challenges, some of which closely resonate with conditions in the South, namely:

1. A lack of appropriate facilities and infrastructure;
2. A lack of appropriately trained clinical scientists and a career structure to support them;
3. Inadequate funding support for experimental medicine and all types of clinical trials;
4. A failure to utilise the opportunity provided by a national health service (NHS) to generate high-quality clinical data for such studies;
5. An increasingly complex and bureaucratic legal and ethical frameworks in the UK and EU.

The lesson to be drawn from the experience of countries with successful research programmes is that government commitment and partnership is indispensable for the innovation of an environment conducive to clinical research, which is well exemplified by the experience of Singapore in the paragraphs that follow. The NHS in the UK, the Department of Health and Social Services (through the NIH) in the US, and the Ministry of Health in Singapore all engage in partnerships with the research community through numerous

channels and at numerous levels in supporting clinical research, such as in the acquisition of research equipment and infrastructure, the funding of the costs of research and the training of clinical researchers, as well as through awards and fellowships to researchers at all levels of seniority in recognition of performance and achievement. The Singapore government has advanced three reasons for committing itself to clinical research – to translate the considerable biomedical research emanating from Singaporean laboratories into clinical applications; to inculcate a knowledge and evidence-based approach to health care; and to retain top medical talent in the public hospitals.

This rationale has so far eluded South Africa, where the trend has been in the opposite direction. As described in Chapter 7, the deliberate withdrawal by provincial health departments in recent years from investing in clinical research-related equipment and infrastructure, combined with the gross under-funding of both research-active hospitals and the main agency for public funding (the MRC) has all but gutted the capacity to conduct clinical research. The severance of pathology laboratories from the public hospitals, consolidating them into the autonomous, fee-for-service NHLS that charges market-related fees for tests performed in the pursuit of research, has significantly increased the cost of clinical research in the face of the extremely limited research funding.

Translating research into policy and practice

Translational research – the purpose of which is to develop new evidence-based therapies for patients, to improve diagnosis and prognosis, and to promote prevention – is of little use unless the resulting evidence-based interventions and techniques are integrated into the health system and adopted by health practitioners. The evidence from the South is that local clinical research outcomes rarely find their way into clinical practice. Such research therefore all too often begins and ends as an academic exercise to generate papers for publication in learned journals. In a paper from Tanzania, Kitua *et al.*, (2000) observe that “neither academic nor medical and health

research institutions in developing countries regard it as their responsibility to communicate their research findings to local policy-makers, practising health professionals, or the public. It is optimistically assumed that key national decision makers will access the relevant publications, understand the research language, select useful, locally relevant results, and use them in planning and implementing sound health programmes" (Kitua *et al.*, 2000).

As detailed in Chapter 8, South African clinical researchers have increasingly elected to publish their work overseas where it is least likely to be read by South African practitioners or policy-makers and thus make an impact on local practice. The inability of clinical research to influence policy in the South cannot, however, be wholly be blamed on researchers. Politicians and policy-makers have often been impervious and even hostile to evidence-based interventions derived from new research, as was glaringly illustrated by the controversies that surrounded HIV/AIDS management and prevention in recent years. In Singapore, Minister of Health Khaw Boon Wan recently conceded that previously, "research (had not been) a priority in Singapore's Ministry of Health. The concern was that clinical research would lead to more costly treatment options. This would increase health care costs and also fan public expectations for esoteric treatment for which our society might not be prepared to pay" (<http://www.moh.gov.sg/mohcorp/speeches.aspx?id=18732>).

Elsewhere in the world, the uptake of clinical research outcomes in policy and clinical practice has hinged on several conditions:

1. There must be a closely **cooperative and mutually trusting relationship** between the researchers and health policy-makers and implementers.
2. There must be a **collaborative forum for clinical researchers** to engage in mutual dialogue, and to empower themselves to lobby government and other stakeholders as a collective. One such model comes from Tanzania. Frustrated by the research community's failure to influence the Tanzanian health policies – for instance in respect of the malaria eradication programme – Tanzanian clinical researchers formed a National Health

Forum, set up to "act as a consultative and advisory body on health research to the policy and decision makers in the Ministry of Health and wider government" (Kitua *et al.*, 2000). The forum has also served to foster greater collegiality among researchers of different affiliations, and closer cooperation among the various research institutions in the country.

The US has numerous **research networks** of clinical research interests and interest groups whose programmes are accessible through the NIH's Inventory for Clinical Research Networks (<http://www.clinicalresearchnetworks.org>). One example of such a forum is the NIH's Clinical and Translational Science Award (CTSA) Consortium, constituted in recognition of the conditions that "are making it more difficult to translate new knowledge to the clinic – and back again to the bench. These challenges are limiting professional interest in the field and hampering the clinical research enterprise at a time when it should be expanding." The goal of the CTSA is "to transform the local, regional and national environment for clinical and translational science. The CTSA is a consortium of institutions bridging basic, clinical and translational research to bring effective strategies and treatments into clinical practice more rapidly."

3. There must be **structured channels** for clinical researchers to share their work with the Ministry of Health and other stakeholders on a regular basis. Such links exist in one form or another in the UK between research organisations and the NHS, and in the US between the NIH (and other research formations) and the Department of Health and Human Services. In South Africa, this would imply a structured and cooperative partnership between the research community, the DoH and other stakeholders such as the MRC and industry.

SOLUTIONS IN THE LITERATURE

To further explore the barriers to clinical research and the remedies that have been applied elsewhere in the world, the Panel has looked at a variety of publications on strengthening clinical research, including those from the

Association of Medical Colleges, the Canadian Institute of Health Research and the UK clinical research collaboration. Google Scholar and other literature sources were also searched using the keywords 'strengthening', 'clinical', 'research', 'barriers' and 'academic medicine'. Table 10.1 summarises the barriers that were identified. These were grouped into three categories: scarcity of skilled clinical researchers, funding and current profile of clinical research. These are further subdivided into sub-categories of specific categories and recommended interventions.

Table 10.1: Barriers to the promotion of clinical research and interventions to address them

Barrier Category	Specific barrier identified by the literature	Recommendations and interventions addressing these barriers
Few skilled clinical researchers	Lack of opportunity to acquire skills and knowledge in medical schools	<ul style="list-style-type: none"> • Develop a combined professional/PhD degree for clinician-scientist graduates such as the MD/PhD (US) or MB/PhD (UK) • Increase institutional support and oversight for clinical research and training
	Attracting new clinical researchers and retaining clinical researchers	<ul style="list-style-type: none"> • Develop mentoring programmes • Provide incentives for student and staff undertaking research • Support the career development of investigators <p><i>E.g. Mentored Patient Orientated Research Career Development Award of the NIH (K23)</i></p>
	Lack of support for senior researchers	<ul style="list-style-type: none"> • Develop long-term funding for those conducting research • Relief from patient care and administration to increase time for research <p><i>E.g. Midcareer Investigator Award in Patient Oriented Research of the NIH (K24)</i></p>

Barrier Category	Specific barrier identified by the literature	Recommendations and interventions addressing these barriers
Funding	Lack of grant schemes in Africa	<ul style="list-style-type: none"> Schemes to be supported within Africa Support for clinical training fellowships through South-South partnerships <p><i>E.g. Kenya and Malawi partnership between the DFID, the IDRC and the Wellcome Trust</i></p>
	Lack of institutional funding	<ul style="list-style-type: none"> Strengthening existing institutions and field sites <p><i>E.g. initiative between the UK's MRC, health departments, Wellcome Trust, Wolfson Foundation, Cancer Research UK and British Heart Foundation to boost experimental research</i></p> <ul style="list-style-type: none"> Funders funding full cost of research when necessary, including developing management and core technical staff <p><i>E.g. South-South and North-South Initiative</i></p>
	Lack of partnerships	<ul style="list-style-type: none"> Develop a forum to coordinate partnerships Promote institutional partnerships Promote partnerships between government, industry and regulators Staff exchange and student partnership
Current profile of clinical research	Lack of research agenda and a mechanism to implement such an agenda	<ul style="list-style-type: none"> Develop an advocacy body to implement a research agenda
	Low recognition by government of research in addressing health issues	<ul style="list-style-type: none"> Government needs to dedicate 2% of GDP for funding of research and development Health information systems need to be supportive of clinical research Establishment of a health entity to drive the clinical research agenda
	Insufficient translation of research into policy and practice	<ul style="list-style-type: none"> Increase funding for reporting and disseminating mechanisms <p><i>E.g. The NIH Institutional Clinical and Translational Science Award (CTSA)</i></p>

FURTHER SOLUTIONS IN THE GLOBAL EXPERIENCE RELEVANT TO AFRICA

Effective government leadership: the British example

A coordinated initiative was launched in the UK in 2005 providing £117 million of new funding from the Medical Research Council (MRC), health departments, the Wellcome Trust, Wolfson Foundation, Cancer Research UK and the British Heart Foundation. Additional investment has subsequently been provided by a number of funding bodies including the Health Research Board of Ireland, resulting in a total of £134 million being provided to boost experimental medicine in the UK and Ireland. The initiative consisted of three separate calls for proposals and throughout the process the UK's Clinical Research Consortium (CRC) funding partners have been working together and sharing information on proposals received. Increased support for experimental medicine research programmes was provided by the MRC. This was complemented by major funding targeted at building up the infrastructure underpinning experimental medicine. Infrastructure was supported through a joint call to fund new clinical research facilities and strengthen existing ones, and also through an initiative to expand a network of experimental cancer medicine centres. Funding decisions have been taken for all three elements of the coordinated initiative, resulting in 28 grants for new experimental medicine programmes funded through the MRC initiative, 11 new awards to establish new and develop existing UK clinical research facilities funded through a Wellcome Trust-led Clinical Research Infrastructure Initiative with a consortium of funders, including the Wolfson Foundation, the MRC, UK health departments, the British Heart Foundation and Cancer Research UK. An additional facility jointly funded by the Wellcome Trust and the Health Research Board of Ireland is being established in Dublin. There are 17 centres assigned as Experimental Cancer Medicine Centres, plus two designated as Experimental Cancer Medicine Centres in Development through a Cancer Research UK/Health Departments call. Taken together, these developments represent a considerable increase in the UK's capability and capacity to conduct high-quality experimental medicine research. However, there is

agreement that they need to facilitate networking between these facilities to provide standardisation and coordination of research practice and provide links with the rest of the national infrastructure. As a first step, the UK Clinical Research Network (UKCRN), under the auspices of the UKCRC, is working closely with the existing clinical research facilities to develop an information system that maps resources and expertise in experimental medicine. Throughout this process the UKCRC has been working closely with industry to ensure that their needs are being taken into account (UK Clinical Research Collaboration Progress Report, 2004-2006).

Effective government leadership: the Singapore example

Singapore presents a striking example of a government that is passionate about clinical research and the development and retention of its researchers. The country has a definite career path for clinician-researchers, and moreover promotes and rewards performance in clinical research through special awards for research excellence. Furthermore, the Ministry of Health is fully committed to the translation and integration of research outcomes into clinical practice in the health service. The commitment sets Singapore apart among the nations of the South, and is evident in the following:

1. The Ministry of Health (MOH), jointly with the National Medical Research Council (NMRC), have ensured that public hospitals are appropriately equipped with the most up-to-date infrastructure to facilitate good clinical research.
2. In order to retain its top researchers, the NMRC and the MOH jointly sponsor awards to recognise and reward senior researchers for excellence in clinical research. These include:
 - The STaR Investigator Award, a prestigious award jointly offered by the MOH, NMRC and the Agency for Science, Technology and Research (A*STAR), to recognise and support outstanding researchers who conduct research that involves integrating basic scientific discoveries with clinical applications;

- The Clinician Scientist Award, which is given to researchers who have demonstrated a sustained, high level of productivity and leadership in translational and clinical research.
3. The NMRC offers capacity-building grants specifically to train clinician researchers, including:
- The NMRC Research Training Fellowship, awarded to outstanding and talented clinicians for overseas research training or to pursue a PhD in research in local institutions and to acquire the qualifications and skills to become Clinician Scientists;
 - NRF-MOH Scholarship to promote clinical and translational research by equipping a select group of Medical Specialist Trainees with the academic qualifications and skills to pursue careers as Clinician Scientists through a structured yet flexible training route;
 - National University of Singapore Scholarship (MOH-funded) to equip clinicians with the basic methodological and practical skills to design and conduct clinical investigations that are relevant to patient care, from new treatments and technologies to diagnostic modalities to effectiveness of health services.

In the words of Singapore's Minister of Health, "Supporting clinical research and knowledge-driven care will help to draw and retain top doctors and medical talent within our public hospitals. I think you have heard this many times both from our own doctors who are interested in research as well as the newly recruited doctors from overseas whom we managed to persuade to return to Singapore. By meeting clinicians' aspirations for scientific discovery, they can develop professionally and be more intellectually engaged in their work. We therefore hope that participation in research programmes will help reduce the brain drain of our doctors to the private sector and to other countries."

Partnerships: examples in Africa

Cross-boundary schemes that are administered within African countries, with national governments contributing in an agreed way, are sorely needed to

nurture promising young scientists to become the research leaders of the future. Awards should be made in open, transparent competition to African institutions with promotion of cross-institutional, multidisciplinary research to build South-South linkages. Support, including training in scientific writing and in translating research results into policy and action, should be provided to promising young scientists to develop competitive proposals so that they are not lost to the system, and substantial re-entry grants are required to attract back scientists who have moved abroad. In some cases support is required for infrastructure and legal changes to improve institutional and national governance to provide an environment in which research can flourish (Whitworth *et al.*, 2008).

One example of an initiative aiming to do this in Kenya and Malawi is the **Health Research Capacity Strengthening Initiative partnership between the Department for International Development (DFID), the International Development and Research Centre (IDRC) and the Wellcome Trust**. Two national task forces have been supported to develop proposals focused on supporting and training individual scientists through local grant-making capacity, strengthening key academic research and policy-making institutions, developing a portfolio of health system research activities and improving regulation and coordination of the national research environment. This initiative aims to re-establish research in African universities as a viable career pathway for young and established scientists, through the support of senior mentors and encouragement of a vigorous research culture (Whitworth *et al.*, 2008).

While African governments have a role in providing at least basic infrastructural support, external funders have often failed to ensure that the full costs of research were generated in developing country institutions. This may include the cost of upgrading infrastructure and support services, such as research management and governance, accounting and financial reporting processes, information technology and library services. For research to flourish, there is a need to recognise that the requisite organisational framework, adequate human resources and access to the appropriate skills and tools are

all required. Therefore, in some cases it is also necessary to fund the career development of management and core technical support staff, and to assist generally with strategic capacity development plans, setting out pathways for capacity strengthening and setting priorities for funding (Whitworth *et al.*, 2008).

The Wellcome Trust has recently launched an **African Institutions Initiative** which aims to build a critical mass of sustainable local research capacity across Africa through strengthening African universities and research institutions. The objectives include creating equitable and sustainable South-South and North-South partnerships and networks between institutions, building a critical mass of local research capacity and developing vibrant research environments geared to national priorities across Africa, supporting the human resources and infrastructure necessary for the administrative, governance, financial and management functions needed for institutions to deliver research excellence, developing and building leadership at individual, institutional and national levels so countries can better initiate and lead research activities, and enthuse young scientists to develop research careers. Awards totalling up to £30 million were made at the end of 2008. In addition, the Wellcome Trust has already made seven Strategic Awards for over £30 million for capacity-strengthening initiatives in Africa and the Indian sub-continent (Whitworth *et al.*, 2008).

An **inter-agency working group** probably needs to be established involving relevant funders in order to maintain contact and promote coordination. Partnerships between African institutions need promoting, especially those between research institutions and universities. Joint appointments, joint supervision and research-predominant posts to give protected time for research, free from a heavy burden of teaching and service commitments, are important ways to bring research institutions and universities closer together. Appropriate and equitable North-South partnerships should be supported. This may require providing training in negotiating skills and strategic plan development. Guidelines and principles to ensure that these are true partnerships and to mitigate power imbalances have been developed and funders should ensure that these are followed to ensure that African institutions

are able to articulate their needs. For example, the **European Developing Country Clinical Trials Programme (EDCTP)** adheres to these principles when assessing funding applications for research partnerships. Other appropriate roles for Northern institutions include staff exchanges, student pairings, teaching, joint degree programmes, and helping to set up facilities and organisational frameworks (Whitworth *et al.*, 2008).

An important requirement for successful partnerships is that mechanisms exist to **track and disseminate the aggregate levels of financial support for clinical research** provided by public funders, industry, foundations, voluntary organisations, health plans and insurers, academic health centres, hospitals, and other health care providers. Data on the funding of and participation in clinical research should be reported regularly by all funding entities and made available to groups with an interest in the vitality of clinical research. A national strategy should also be developed for a public-private sector partnership to fund the creation of broad-based clinical information systems. A substantial investment is needed to meet the requirements of health services and population-based research and the advancement of evidence-based medicine (Association of American Medical Colleges, 1999).

High-profile **advocates** are required and this could be a role for revitalised national academies of science, the Network of African Science Academies, the African Academy of Science and the African Union, among other bodies. There is a need to agree with politicians and policy-makers on how science and technology can contribute to achieving the Millennium Development Goals, to development more generally, and to wealth creation from product development through partnerships with industry and entrepreneurs. African governments need to better appreciate the benefits of research and to be prepared to commit dedicated funding to national budgets (Whitworth *et al.*, 2008).

Developing coordinated research agendas and implementing them

Funders can ensure that Northern institutional partners develop long-term **sustainable partnerships** and support South-South networks so that

established institutions can assist the development of emerging institutions, as has been the ethos behind recent Wellcome Trust initiatives for capacity strengthening. African research centres need long-term support to be able to grow organically over time (Whitworth *et al.*, 2008).

One good example of an advocacy body is **the Initiative to Strengthen Health Research Capacity in Africa (ISHReCA)** which was established following the meeting in Kilifi, Kenya, which brought together health researchers in Africa to promote the creation of self-sustaining pools of excellence capable of initiating and carrying out high-quality health research in Africa. Their mission also includes translating research products into policy and practice through better integrated approaches to capacity building at individual, institutional and system level. ISHReCA aims to provide a platform for African health researchers to discuss the need for health research capacity building, to promote an African-led agenda and negotiate this with funders and partners, to advocate for increased commitment of national governments and civil society and to reinforce at the regional and international level the urgency for networking and building capacity for health research in Africa (Whitworth *et al.*, 2008).

The **Ifakara Trust model** has over decades developed from a site reliant on a Northern partner for scientific and administrative drive, with a small number of independent project grants, to an independent centre with a scientific board, which derives core funding from a large number of grants for individual projects for long-term stability. In this way each project contributes to core costs, but there is also a core grant to sustain the centre, support independence and avoid chasing grants regardless of whether they fit the strategic priorities. International funders should consider providing core funds to assist the development of field sites to become mature centres that can address national and international research priorities through research, training and service provision (Whitworth *et al.*, 2008).

Recognition by governments of the value of research in addressing health issues

Important lessons can be learnt from the **review conducted by Cooksey (2006)**, which recommended that the UK government should seek to achieve better coordination of health research and more coherent funding arrangements to support translation by establishing an **Office for Strategic Coordination of Health Research (OSCHR)**. The office will report jointly to the Secretaries of State for the Department of Health and the Department of Trade and Industry, and will allow for strategic input from the Health Departments from the devolved administrations. The review recommended that the effectiveness of the joint reporting arrangements in practice should be reviewed in 2011 (Cooksey, 2006).

It is essential that **health information systems** are supportive of clinical research (Silverman, 2004). In 1997, some national governments began taking action to introduce research-led practice in their countries. In Chile, the Ministry of Health has established, with support from the European Union, an office to promote the implementation of research findings. In Palestine, doctors are working with the health minister to establish a national committee on clinical effectiveness. In Thailand, the Ministry of Health and the National Health Services Research Institute are setting up an office to guide a national quality assurance programme. In South Africa, the MRC has committed support to the production of systematic reviews and evidence-based practice. In Zimbabwe and South Africa, researchers are working with their governments to test ways of getting research into policy and practice. In the Philippines, the Department of Health has funded projects to develop evidence-based guidelines for its cardiovascular disease prevention programme (Garner *et al.*, 1998).

Improved translation of research into practice

Increased funding for clinical research infrastructure and the establishment of reporting, tracking and disseminating mechanisms for clinical research are essential for strengthening clinical research. In the UK, translational research was recommended to be the joint responsibility of the Medical Research

Council-National Institute for Health Research (MRC-NIHR) with the strategy overseen by a new Translational Medicine Funding Board and joint working facilitated by the OSCHR, with MRC technology continuing to play a key role (Cooksey, 2006).

It is important to disseminate research findings to a variety of audiences, including other health professionals, lay readers, and journalists. Many mechanisms for implementing good practice are already available in developing countries. In some, guidelines and standardised treatment manuals are better developed than in the West. Other guidelines are likely to become more evidence based over time. Reviews of specific interventions to change professional practice, such as those by Bero *et al.* and those presented by Ross-Degnan *et al.* (International conference on improving the use of medicines, Chiang Mai, Thailand, April 1997), will help to ensure that change occurs, but dissemination efforts in developing countries need further evaluation (Garner *et al.*, 1998).

There are a variety of new initiatives to encourage practitioners and policy-makers to assess and implement research evidence. Some clinicians examine variations in practice between themselves, for example in Thailand. A framework to assist clinicians to apply research evidence to their practice was developed in Chile at the Santiago seminar for getting research into policy. In the Philippines, an ongoing study is looking at the use of standardised clinical encounters in evaluating practice variation. Another mechanism being investigated through the Reproductive Health Library is to ask health professionals how they would use the results from a particular systematic review in their practice of reproductive health; if successful, this intervention could be used in other clinical specialties (Garner *et al.*, 1998).

The barriers to strengthening clinical research have been discussed, and from what has been said above, it is evident that some barriers have been more adequately addressed than others. It is our hope that these models will lay the foundation for a South African model which would suit our context.

THE OVERALL LESSONS LEARNT

What has been shown in many countries is that transforming the relationship between clinical research and society is a serious and difficult undertaking, but one that stands to yield enormous dividends. Funding and implementing the programmes necessary to achieve this success require a commitment from diverse constituencies and strong confidence in the value of doing so. While large-scale programmes are expensive, the pay-off in the form of more efficient identification of the causes of illness and of both effective and ineffective therapies can relieve much of the financial burden. The funds saved by accelerating recruitment and reducing research delays may also be substantial. With fewer delays, study results are available more quickly, allowing faster progression to the next research step and accelerating the process of discovery and validation. Wider public involvement promotes greater support and funding for health-related research. Honest inquiry in the form of clinical research, aligned across all sectors of society, rewards participants, clinicians, the research community and society as a whole. It is our collective responsibility to integrate clinical research into the broader social context, helping it to achieve its full potential (Avins and Goldberg, 2007).

FINDINGS

1. Although health research, and especially clinical research, is acknowledged as indispensable for improving health, promoting equity and stimulating development, it tends inexplicably to be neglected in sub-Saharan Africa in terms of planning, status and funding.
2. Much attention has been paid to promoting clinical research in the North, in the face of challenges similar to those afflicting the South, so it is possible that solutions already found elsewhere can also be applied here. These include maintaining the supply of skilled clinical researchers, improving facilities for clinical research, increasing funding and strengthening translational research.

RECOMMENDATIONS

1. Government commitment and partnership is needed to revitalise clinical research. The Singapore government, for example, invests in clinical research to translate the biomedical research emanating from its highly competitive research institutes into clinical applications; to inculcate a knowledge and evidence-based approach to health care; and to retain the highest level of medical talent in the public hospitals.
2. There must be a closely cooperative and mutually trusting relationship between researchers and health policy-makers and implementers. The NHS in the UK, the Department of Health and Social Services (through the NIH) in the US, and the Ministry of Health in Singapore all engage in partnership with the research community through numerous channels and at numerous levels to support clinical research.
3. Efforts should be targeted at building indigenous research capacity. Singapore has a definite career path for clinician-researchers, and promotes and rewards performance in clinical research through special awards for research excellence.
4. High-profile advocates are required to promote clinical research. One example of an advocacy body is the Initiative to Strengthen Health Research Capacity in Africa (ISHReCA), bringing together health researchers in Africa to promote the creation of self-sustaining pools of excellence capable of initiating and carrying out high-quality health research in Africa.
5. Better strategic planning and coordination for health research is required. An example of such an initiative is the Health Research Capacity Strengthening Initiative partnerships in Kenya and Malawi.

REFERENCES FOR CHAPTER 10

- Academy of Medical Sciences. 2003. *Strengthening Clinical Research*. Available at: <http://www.acmedsci.ac.uk/images/publication/pscr.pdf>.
- Association of American Medical Colleges (AAMC). 1999. *Breaking the Scientific Bottleneck. Clinical Research: A National Call to Action*. Washington DC: AAMC report.
- Avins, A. L. and Goldberg, H. 2007. *Creating a culture of research*. *Contemporary Clinical Trials*. 28: 557-562.
- Cooksey. 2006. *A Review of UK Health Research Funding*. Norwich: Crown. pp. 1-7.
- Garner, P., Dickson, R. and Salinas, R. 1998. *Implementing research findings*. *British Medical Journal*. 317: 531-535.
- Kitua, A. Y., Mashalla, Y. J. S. and Shija, J. K. 2000. *Coordinating health research to promote action: The Tanzanian experience*. *British Medical Journal*. 321: 821-823.
- Nchinda, C. T. 2002. *Research capacity strengthening in the South*. *Social Science and Medicine*. 54: 1699-1711.
- Promoting Clinical Research in Public Hospitals (An address by the Minister of Health – Khaw Boon Wan, Singapore, 26 May 2008)*. Available at: <http://www.moh.gov.sg/mohcorp/speeches.aspx?id=18732>.
- Silverman, M. 2004. *A Roadmap to Ensure Canadian Leadership in Clinical and Translational Research*. Canadian Institutes of Health Research (CIHR), Canada.
- Translational Research – Overview National Institutes of Health (NIH)*. Available at: <http://www.nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>. Accessed on 5 June 2009.
- UK Clinical Research Collaboration. 2007. *Progress Report 2004-2006*.
- Whitworth, J. A. G., Kokwaro, G and Kinyanjui, S. 2008. *Strengthening capacity for health research in Africa*. *Lancet*. 372 1590-1593.

CHAPTER 11:

KEY FINDINGS AND RECOMMENDATIONS – WHAT ARE THE KEY BARRIERS? WHAT ARE THE SOLUTIONS (POLICY INTERVENTIONS)? WHO IS RESPONSIBLE FOR SOLVING THE PROBLEM?

WHAT ARE THE BARRIERS TO THE CLINICAL RESEARCH ENTERPRISE IN SOUTH AFRICA?

1. Inadequate public engagement with clinical research

- Government does not promote clinical research sufficiently in the public domain;
- Researchers do not engage sufficiently with issues of importance to research participants and policy-makers.

2. Lack of research planning, regulation and coordination

- Lack of a coordinated national plan to balance excellence on the world stage (i.e., quality and impact) with relevance to local problems;
- Inefficient regulatory framework for clinical trials and registration of new medicines is hindering the conduct of innovative clinical trials.

3. Inadequate capacity for clinical research (human resources and infrastructure)

- Poor teaching and matriculation rates in mathematics and science in schools;
- Lack of appropriately trained clinical scientists and career structure to support them (i.e. 'frozen demographics' of ageing white male clinical scientists with too few young, black and woman researchers);
- Lack of appropriate facilities and infrastructure (i.e. virtual absence of dedicated clinical research centres).

4. Lack of adequate and appropriate funding

- Inadequate funding for clinical trials and other types of clinical research (e.g. MRC project grants have an upper limit of R130 000 p.a.);
- Cost-recovery regime of the provincial department of health and the National Health Laboratory Service prohibits investigator-driven, non-industry clinical research in academic health complexes.

5. Absence of monitoring and evaluation

- No monitoring of adherence to standards and performance of individual researchers, academic institutions, research councils, government departments, health industry and other funders of research.

WHAT ARE THE MAIN SOLUTIONS?

1. National Strategic **Planning, Regulation** and **Coordination** of clinical research

- We propose the formation of a **South African Clinical Research Coordinating Centre** by the MRC to serve as an advocacy group and a partnership of organisations working to establish South Africa as a world leader in clinical research by harnessing the power of all stakeholders, including universities, government departments, the National Health Laboratory Service, the health industry and research councils.
- The proposed **Coordinating Centre** should be accorded maximum operational independence, while remaining fully accountable in the overall sense. Its composition and terms of reference should be carefully designed in order to provide it with a maximum chance of success in its specific operating environment.
- The proposed **Coordinating Centre** should engage with the **National Health Research Committee** on how optimal planning, regulation and coordination of clinical research may be achieved, in consultation with the Departments of Health, Higher Education, Science and Technology, and Trade and Industry.
- The proposed **Coordinating Centre** should interact with the newly established National Planning Unit in the Presidency on the planning needs of clinical and health research.
- The proposed **Coordinating Centre** should seek to play an advisory role to the proposed Medical Regulatory Authority (successor to the Medicines Control Council) and the National Ethics Committee in order

to deal with the regulatory environment and ethical oversight for clinical trials and health research in general.

- The proposed **Coordinating Centre** should ensure the alignment of the clinical and health research effort with the principles of essential national health research and other policies of the government.
- The proposed **Coordinating Centre** should oversee the maximisation of intellectual property development in and by the clinical research system.

2. Human and Infrastructural Capacity

- Towards a **National Clinical Scholars Programme** as part of the Ten-Year Innovation Plan of the DST:
 - A target of 500 PhDs to be produced in clinical health sciences over the next 10 years as part of the plan by the DST to increase the graduation rate of PhDs in general to 6 000 per year between 2008 and 2018, plus a target of 150 postdoctoral fellows per annum working in South African clinical research environments.
 - A target of 30 Research Chairs in clinical research areas to help tackle the 'Farmer to Pharma' grand challenge and other strategic areas.
- The creation of **Clinical Research Centres and Research Institutes** as national hubs in the academic health complexes and other sites:
 - Develop a National Joint Agreement between universities and the Departments of Health, Education and Science and Technology, in order to provide a 'research platform' alongside the clinical and teaching platforms in the academic health complexes and other sites.
 - Create a **National Clinical Research Training Coordinating Initiative** to link and coordinate clinical research training at universities, research councils, government and industry. This initiative will serve as a warehouse of education and training opportunities

(i.e. projects, funding, courses, degrees) and a meeting place for supervisors and potential students at national level.

- Establish attractive, high-capacity training programmes for undergraduate and postgraduate students in the clinical health sciences, as well as for junior faculty in clinical research, as part of the human capital generation project of the DST's Ten-Year Plan.
- Fund learnerships for graduates in the research facilities of large multinational companies.
- Foster a clinical-plus-research academic career track (lectureships and professorships) in all clinical disciplines in South African institutions.
- Develop and support a network of skilled mentors who can lead the development of young clinical researchers.

3. National Funding Scheme for Clinical and Health Research

- Raise the national R&D budget to 2% of the GDP, of which 20% should be allocated to health research (DST).
- Implement the Mexico declaration commitment by the national Department of Health to spend 2% of the national health budget on research and development, and amend the Research and Development Tax Incentives Policy to encourage innovative R&D in South Africa by removing the exclusion of clinical trials (DTI).
- Incentivise the health care industry (pharmaceuticals and private hospitals) to spend 2% of their turnover on research and development (pharmaceutical manufacturers and others).
- Follow up on the recently implemented Clinical Training Enhancement Initiative with a well-aligned approach to clinical research training.

4. Monitoring and Evaluation of the Clinical and Health Research Enterprise

- Evaluation of the performance of the clinical research enterprise in South Africa, possibly by the Academy of Science of South Africa, by

reviewing the implementation of the recommendations of this report at five-yearly intervals.

- Monitoring by the National Health Research Committee of the efficiency of research expenditure of the MRC and other statutory bodies entrusted with health research.
- Monitoring audit by the new Monitoring and Evaluation Unit in the Presidency of the government ability to meet the target of spending 2% of GDP on research and development, and 2% of the health budget on health research.

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APPENDIX A:

BIOGRAPHICAL SKETCHES OF THE STUDY PANEL

**Professor AMABOO (AMES) DHAI, MB ChB, FCOG, LLM,
PGDipIntResEthics**

Professor Dhai obtained her MB ChB degree from the University of KwaZulu-Natal. She specialised as an Obstetrician and Gynaecologist through the Colleges of Medicine of South Africa; she is a Fellow of the College of Obstetricians and Gynaecologists (FCOG). She subsequently obtained a Master's degree in Law (LLM) from the Law School of the University of KwaZulu-Natal, and a Diploma in International Research Ethics from the University of Cape Town. She was appointed Head of Bioethics, Medical Law and Research Ethics at the Nelson R Mandela School of Medicine at the University of KwaZulu-Natal in 2004. In January 2006 she took on the position of Head of Bioethics at the University of the Witwatersrand Medical School and is serving as the Director. Her special interest is research ethics. She served as chairperson of the Research Ethics Committee of the University of KwaZulu-Natal for two years, and as a member of the Interim National Ministerial Research Ethics Committee between 2002 and 2005, and in 2006 was appointed Deputy Chair of the National Health Research Ethics Council. She serves on the MRC Ethics Committee, established and chairs the Hospice Palliative Care of South Africa Research Ethics Committee and is co-chair of the Wits Human Research Ethics Committee (Medical). She also serves on the Medical and Dental Professions Board of the Health Professions Council of South Africa, is a member of the Council of the College of Obstetricians and Gynaecologists of South Africa, and is a member of the Human Rights, Ethics and Professional Development Committee of the Health Professions Council. Her publications in the main are on bioethics and medical law.

**Professor PETER FOLB, MB ChB, MD, FCP SA, FRCP Lond, FRSSAf,
MASSAf**

Professor Folb has a doctorate in pharmacology and is a Fellow of the Royal College of Physicians, London (FRCP Lond). Previously he was a Senior Lecturer in Clinical Pharmacology at the University of London at Guy's Hospital and Professor of Pharmacology at the University of Cape Town. From 1980 to 1998

he served as chair of the South African Medicines Control Council, the national drug regulatory authority. He has supervised more than 80 postgraduate students, and has served as a consultant to the World Bank, *Médecins Sans Frontières* and as expert adviser to the World Health Organisation (WHO) over many years. From 1996 to 2004 he chaired the WHO special task force for research into severe malaria, and from 1998 to 2004 he chaired the WHO scientific advisory committee on vaccine safety. Peter Folb has served, *inter alia*, as a member of the WHO Strategic Advisory Group of Experts (SAGE) on vaccine policies worldwide and as a member of the WHO/TDR proof of principle committee, which directs the scientific and strategic development of new drugs for neglected tropical diseases. He was previously co-director of the South African Medical Research Council Traditional Medicines Research Unit, based jointly at the University of Cape Town and the University of the Western Cape. From 1994 to 2003 he was director of the WHO Collaborating Centre for Drug Policy Research. For many years he was co-editor of *Meyler's Side Effects of Drugs* – the international encyclopaedia of adverse drug events. His special interests are in the fields of clinical and experimental pharmacology, drug safety and the scientific basis of new drug development. He is a Fellow of the Royal Society of South Africa, a Fellow of the University of Cape Town and a Member of the Academy of Science of South Africa (ASSAf). He has published extensively and has authored three books on drug safety. Since 2004 he has been Chief Specialist Scientist at the South African Medical Research Council.

Professor WIELAND GEVERS, MB ChB, MA, DPhil, DSc *honoris causa*, FCP SA *ad eundem*, MASSAf, FTWAS

Professor Gevers qualified in medicine in 1960, and proceeded as a Rhodes Scholar to Oxford University where he obtained the DPhil degree in 1966 under Sir Hans Krebs (regulation of liver metabolism). He subsequently spent four postdoctoral years in the laboratory of another Nobel Prize winner, Dr Fritz Lipmann, at the Rockefeller University in New York (biosynthesis of peptide antibiotics) before returning to South Africa in 1970. He was Senior Deputy Vice-Chancellor responsible for planning and academic process at the University

of Cape Town from 1992 to 2002, and Professor of Medical Biochemistry since 1978. He was (founder) President of the South African Biochemical Society from 1975 to 1976, and again President from 1981 to 1982. He was President of the Academy of Science of South Africa (ASSAf) from 1998 to 2004. He is a Fellow of the Third World Academy of Sciences (elected 2002). He holds a Distinguished Teacher's Award from the University of Cape Town. Prof. Gevers directed MRC research units at both Stellenbosch University (1970–1977) and the University of Cape Town (1979–1994), using biochemical, cell-biological and molecular genetic approaches to heart contractility, intracellular protein turnover and cholesterol metabolism. He was awarded the Wellcome Gold Medal for Medical Research and the Gold Medals of both the South African Society for Biochemistry and Molecular Biology, and the South African MRC. After his formal retirement from UCT at the end of 2002, Prof. Gevers took up an appointment until 31 March 2005 as the Interim Director of UCT's Institute of Infectious Disease and Molecular Medicine (IIDMM). He was the Executive Officer of ASSAf (until 2008) and he is now the General Secretary of the Academy.

Professor GREGORY HUSSEY, MB ChB, MMed, MSc, DTM&H, FFCH, MASSAf

Professor Hussey has had postgraduate training in paediatrics, public health and infectious diseases, and is registered as a sub-specialist in infectious diseases. He was appointed as Director of the Institute of Infectious Diseases and Molecular Medicine (IIDMM) at the University of Cape Town (UCT) in 2005. Prior to that, he was Professor and Head of Paediatric Infectious Diseases in the School of Child and Adolescent Health at UCT and a consultant to the Red Cross Children's Hospital in Cape Town. His main research interest has been in the field of vaccine-preventable diseases and he has published extensively on this subject. He is currently Director of the South African Tuberculosis Vaccine Initiative whose mandate is to contribute to the development of novel TB vaccines. This initiative is funded by a number of groups, including the Gates Foundation via the Aeras Global TB Vaccine Foundation, the European Union and the US National Institutes of Health. He has been a part-time WHO

consultant for over a decade and serves on a number of international and national committees, including the WHO Tuberculosis Vaccine International Advisory Group, the WHO Global Advisory Committee on Vaccine Safety, the GSK International Data Safety Monitoring Committee for a new rotavirus vaccine and the South African National Advisory Group on Immunisation. Prof. Hussey is actively involved in postgraduate education and training and capacity development of health workers. He is the coordinator of the annual week-long residential course "Developing expertise for vaccinology in Africa". In addition he is the holder of an NIH Fogarty International Global Infectious Disease Research Training Program for the period 2006 to 2010.

Ms MAUREEN KIRKMAN, BSc (Pharm)

Ms Kirkman obtained her BSc in Pharmacy from Rhodes University. After two years in dispensing at the SAR&H Sick Fund and retail pharmacy, she moved in 1966 to the pharmaceutical industry as Managing Director, Technical & Regulatory at FBA Pharmaceuticals (now better known as Bayer Pharmaceuticals) with responsibility for production, packaging, quality assurance and regulatory affairs, including patents and trade marks. In 1987 she joined Adcock Ingram, initially as the Regulatory Affairs Manager with responsibility for the registration of medicines and for regulatory compliance issues. In 1994 she became Strategic Regulatory Affairs Manager in the Adcock Ingram Group R&D Division responsible for strategic regulatory issues, which included planning the regulatory strategy and the regulatory aspects of clinical research, development and registration of new drugs internationally. These included the development of new molecules. In 1997 she joined PMA as Head: Scientific and Regulatory Affairs. This included all the aspects of new legislation that could affect the pharmaceutical industry, including the regulation and control of medicines, labour, training and marketing issues, and liaison with the Departments of Health and Trade and Industry, and with other trade and professional associations. She has been involved in various industry bodies and specialist working groups for many years, including the PMA Science and Technology Committee (SCITECH); PASA Legislative and Self-regulatory Committees for OTC (over-the-counter) medicines, the SAPRAA

Committee, the IMM Advisory Board for the Health Sector, LAAPI – the Labour Affairs Association of the Pharmaceutical Industry – and various industry expert working groups. Recently she was involved in the Industry Task Group set up in 1999 to liaise with the MCC on issues affecting the pharmaceutical industry. She retired at the end of 2008 and now serves as an executive consultant for PIASA.

Dr NONHLANHLA MADELA-MNTLA, BCur, MCur, DCur, Cert. in Advanced Health Management, Diploma in Health Outcomes Research

Dr Madela-Mntla obtained a BCur degree from MEDUNSA (1987), followed by MCur and DCur degrees from the then Rand Afrikaans University (1990–1995). She also has a certificate in Advanced Health Management from the University of Pretoria, a Diploma in Health Outcomes Research and Certificate in Ethical Issues in Clinical Research, the latter two from the Vienna School of Clinical Research, Austria. Her MSc Med Pharmacology is currently on hold after she completed the first two years. She is currently the Executive Manager for Human Capital Management and Development (HCMD) of the MRC. Her role involves human capital development for research (including disbursement of grants and facilitating training opportunities) within the MRC and for the wider academic and health research sectors, while also ensuring transformation in the human resource management processes and policies. She has worked as a health care consultant in research and training (Oasis Resources). She has also headed the Hospital and Community Mental Health Sub-directorate and later the Directorate of the Mental Health and Substance Abuse (1997–2004). She was a lecturer in psychiatric nursing and family medicine (at MEDUNSA) (1995–1997). She has served as a member of the National Essential Drugs Programme (EDP) Committee of the Department of Health. She is a former member of the Board of Psychology of the Health Professions Council of SA (HPCSA) (2003–2004). She is a reviewer for a number of committees for clinical research and grant disbursement. She is a South African representative of the ISHReCA (Initiative for Strengthening Health Research Capacity for Africa) Committee, an all-Africa committee established to interact with funders to coordinate capacity-strengthening initiatives in Africa. The Committee is

mainly funded by the Wellcome Trust, Sida, TDR and other international funders of various activities. She has published and presented papers both locally and internationally, and written chapters in two nursing science books.

Professor BONGANI M MAYOSI, BMedSci, MB ChB, FCP SA, DPhil, FESC, FACC, FRCP, MASSAF

Professor Mayosi graduated with a BMedSci (1987) and MB ChB (1990) from the University of Natal, and trained in medicine and cardiology in Cape Town. He was admitted to the Fellowship of the College of Physicians of South Africa in 1995. In 1998, he was awarded the Nuffield Oxford Medical Fellow to read cardiovascular genetics at the University of Oxford (PhD thesis: *Genetic determination of cardiovascular risk factors in families*). He returned to the University of Cape Town (UCT) and Groote Schuur Hospital (GSH) in 2001 where he continues to work as a physician, teacher and researcher in internal medicine and cardiology. He was promoted *ad hominem* to the rank of Associate Professor of Medicine in 2003, and in 2006 he was appointed Professor and Head of the Department of Medicine at UCT and GSH. His academic work focuses on heart diseases of the poor, i.e. cardiomyopathy, tuberculous pericarditis and rheumatic fever. Uniquely, he employs a wide range of investigative approaches, from molecular to clinical to population-based methods in his efforts to improve the understanding and control of these health problems. In addition, he is at the forefront of efforts to close the 'know-do' gap with respect to heart diseases of the poor, encouraging policy-makers to increase investment in evidence-based control programmes. Professor Mayosi is an established international leader in his field. In 2005, he was awarded the National Research Foundation President's Award (or 'P' rating) and was elected to the Membership of the Academy of Sciences of South Africa. He has been the president of the South African Heart Association since 2007. He has published extensively and has done many reviews.

Professor LETTICIA MOJA, MB ChB, MMed (O&G), MBA

Professor Moja obtained her MBA degree from the University of the Free State. She served as the Dean of the Faculty of Health Science at the University of the

Free State from 2003 until mid-2009, after fulfilling the role of Vice-Dean of the faculty from 2002. She is the first black woman to have headed a South African medical faculty. Prior to this she headed the Gynaecologic Oncology Unit at Ga-Rankuwa Hospital in Pretoria from 1997 to 2002. She firmly believes in the great need for training of health professionals, particularly from disadvantaged communities. She is passionate about unity and harmony while maintaining cultural differences, and is held in high regard by a broad cross-section of colleagues both young and old. She also serves on the Medical and Dental Board and is the Vice-President of the Health Professions Council of South Africa. She was the recipient of the Shoprite Checkers Woman of the Year Award (2004) and was also Chairperson of the National Committee of Medical Deans. She has taken up the post of Principal and Deputy Vice-Chancellor at the University of Limpopo, MEDUNSA campus (as of August 2009).

Professor JAGIDESA (JACK) MOODLEY, MB ChB, FCOG, FRCOG, MD

Professor Moodley obtained his MB ChB from the University of Natal in 1969. He is a Fellow of the Colleges of Medicine (O&G) and the Royal College of O&G (UK). He obtained his MD degree (thesis: *Aspects of the pathophysiology of pre-eclampsia in African women*) from the University of Natal in 1989 and is also a fellow at this university. He is currently an Emeritus Professor at the University of KwaZulu-Natal and is involved in research in the Women's Health and HIV Research Unit. His special interest is high-risk obstetrics, particularly in the aetiology and management of hypertensive disorders of pregnancy. Other interests include perinatal HIV, maternal mortality and audit in obstetric practice. In the past he has held numerous positions, and most recently he served on the Research Ethics Committee of the University of KwaZulu-Natal. He has also served on a number bodies and committees. Currently he is the Chairperson of the National Department of Health's Committee on Confidential Enquiries into Maternal Deaths (NCCEMD) and a member of the National Essential Drug List Committee (NEDLC). He is the advisory board editor for the *European Journal of Obstetrics and Gynaecology and Reproductive Biology*, Elsevier, reviewer for *MRC (SA) Women's Health* and the *International Journal of Gynecology & Obstetrics* and corresponding editor,

Editorial Board, for the *Journal of Obstetrics and Gynaecology*. He was a finalist in the National Science and Technology Awards (2004) for Outstanding Contribution to Science, Engineering and Technology, in the category of Senior Black Researcher over the last 5–10 years. In 2006 he received the FIGO (International Federation of Gynecology and Obstetrics) Distinguished Service Award. He has over 300 publications to his name.

Professor DANIEL NCAYIYANA, MD, FACOG, FCM, MASSAf

Professor Ncayiyana obtained his medical degree from the University of Groningen Medical School, Holland, in 1970. Following postgraduate training at the Albert Einstein College of Medicine and the New York University medical school, he was Board-certified by the American Board of Obstetrics and Gynaecology, was elected Fellow of the American College of Obstetrics and Gynaecology (FACOG), and practiced in the US for 10 years. Back in South Africa (1983), he worked at Rietvlei Hospital and as Chief Medical Superintendent of Umtata General Hospital. He served as Dean of Health Sciences, and later Vice-Chancellor of the University of Transkei. Subsequently, he was Deputy Vice-Chancellor at UCT from 1996 to 2001 and Vice-Chancellor of Durban University of Technology from 2001 to 2005. Prof. Ncayiyana has been editor of the *South African Medical Journal* since 1993; he serves on the Editorial Board of the *British Medical Journal* and the web-based *Medscape*, and is chair of the Editorial Board of the Human Sciences Research Council (HSRC) Press. He is the founder member and first secretary of the World Association of Medical Editors (WAME), and is also a founder member of the Forum for African Medical Editors (FAME). He is an Honorary Fellow of the Colleges of Medicine of South Africa (FCM SA) and a Member of the Academy of Science of South Africa (MASSAf), and has been honorary Professor of Obstetrics and Gynaecology at the universities of Cape Town and Kwa-Zulu Natal. He has previously served as consultant in higher education governance and strategic planning in a variety of sub-Saharan African countries on behalf of the World Bank, USAID and the American Council on Education, the Ford Foundation and in health-related projects on behalf of the WHO. He is advisor to the President/CEO of the HSRC. He has published extensively.

Professor WILLIAM PICK, MB ChB, MMed, FFCH (CM), MFGP, DPH, DTM&H, MASSAf

Professor Pick obtained his MB ChB from the University of Cape Town where he also specialised in Community Health and later became a senior specialist. Professor Pick was Head of the School of Public Health at the University of the Witwatersrand and Chief Community Physician at the Johannesburg Hospital until his retirement in April 2003. He has served as a member of the Health Professions Council, the MRC Board and the Board of the Health Systems Trust for a number of years. He is a Fellow of the Royal Society of Medicine, a Fellow of the Royal Society of Tropical Medicine and Hygiene, a former Fellow of the King's Fund, and held membership of the American Association for the Advancement of Science and the New York Academy of Sciences. In 1990 he was awarded a Fellowship in International Health on the Takemi Program at Harvard University, to which programme he returned as a Visiting Fellow in 1996. He also served as temporary advisor to the WHO on a number of occasions. In 1994 he chaired the ministerial committee on Human Resources for Health Care in South Africa and in 2000 led the task team that prepared the national strategy for Human Resources for Health. He has published widely, and served on the editorial boards of a large number of journals. Currently Professor Pick is the Chairperson of the Council for Medical Schemes. He is also past-President of the MRC and is a Member of the Academy of Science of South Africa.

Dr NANDI SIEGFRIED, MB ChB, MPH (Hons), FCPHM, DPhil

Dr Siegfried obtained her MB ChB degree at the University of Cape Town in 1993 and a Master's degree in Public Health (Honours) at the University of Sydney (2000), and holds a Fellowship in Public Health Medicine (2004). She was a Nuffield Medical Fellow at the University of Oxford from 2004 to 2007, where she was based at the Clinical Trials Service Unit, obtaining a DPhil degree in Clinical Epidemiology. She is a public health specialist and is currently Co-director of the South African Cochrane Centre based at the MRC. She is an active member of the international organisation, the Cochrane Collaboration,

and in 2000 established the Cochrane HIV/AIDS Mentoring Programme to train novice African researchers in meta-analytic methods. Her current research focuses on the methodological quality and conduct of randomised controlled trials of HIV/AIDS interventions and explores the feasibility and sustainability of a national trials support centre to enhance the quality and conduct of trial research in the South African public sector.

Professor JIMMY VOLMINK, BSc, MB ChB, DCH, MPH, DPhil, MASSAf

Professor Volmink obtained his BSc and MB ChB degrees from the University of Cape Town (UCT). He worked as a medical officer and district surgeon, among other posts. He obtained his master's degree in public health from Harvard, following which he was awarded a Nuffield medical fellowship (1993) and completed a doctorate in cardiovascular medicine at the University of Oxford. He is currently Professor and Deputy Dean (Research) at the Faculty of Health Sciences, Stellenbosch University, and Co-Director of the South African Cochrane Centre, MRC. Previous appointments include GlaxoWellcome Chair of Primary Health Care at UCT and Director of Research and Analysis at the Global Health Council, Washington, DC. Prof. Volmink has a special interest in rigorous evaluation of the effects of health care interventions. He has extensive experience in the application of randomised controlled trials, systematic reviews and meta-analysis in evaluating strategies and therapies for the control of tuberculosis, HIV/AIDS and cardiovascular disease. He has worked with policy-makers and clinicians both globally and in South Africa to promote the use of research evidence in making decisions about health care and has taught courses in evidence-based health care to students, health professionals and policy-makers in many countries. He has authored more than 100 peer-reviewed journal articles and book chapters. He serves on committees and advisory boards of a number of international organisations, including the Wellcome Trust, WHO, the Cochrane Collaboration, the Vienna School of Clinical Research and the Belgian Red Cross. He is also a member of the advisory boards of a number of international journals and serves as a peer referee for several others. He is a Member of the Council of the Academy of Science of South Africa.

APPENDIX B:

ABOUT THE ACADEMY OF SCIENCE OF SOUTH AFRICA

THE ACADEMY OF SCIENCE OF SOUTH AFRICA ACT (2001): A STATUTORY BODY PLACED STRATEGICALLY IN THE NATIONAL SYSTEM OF INNOVATION

The Academy of Science of South Africa (ASSAf) was inaugurated in May 1996 in the presence of **then President Nelson Mandela, the patron of the launch of the Academy**. It was formed in response to the need for an academy of science consonant with the dawn of democracy in South Africa: activist in its mission of using science for the benefit of society, with a mandate encompassing all fields of scientific enquiry in a seamless way, and including in its ranks the full diversity of South Africa's distinguished scientists. The South African Parliament subsequently passed the **Academy of Science of South Africa Act, Act 67 of 2001**, which came into effect on 15 May 2002. ASSAf is thus the official national Academy of Science of South Africa, recognised by Government and representing South Africa in the international community of science academies.

Internationally recognised science academies are similar in that they are:

- **self-perpetuating**, with a merit-based membership that creates an upward aspiration for quality and excellence in scientific endeavours;
- **multidisciplinary**, striving to represent science as a continuum of knowledge, insight and practical solutions;
- **independent of government**, but can be funded by government for performing certain tasks;
- a **credible voice of science** to be heard on topics of national concern, independent of institutional or commercial linkages, obligations and agendas;
- linked together in an **independent global community** that can mobilise scientific thinking, skills and knowledge across the world.

ASSAf places particular emphasis on **excellence in the application of scientific thinking to the problems and challenges facing South African society**. It draws its membership from all population groups and from all scientific disciplines.

OBJECTIVES

Scientific thinking for the good of society

According to the Act, the **objectives of the Academy** are to:

- promote common ground in scientific thinking across all disciplines, for example the physical, mathematical, life, human, social and economic sciences;
- encourage and promote innovative and independent scientific thinking;
- promote the optimum development of the intellectual capacity of all people;
- provide effective advice and facilitate appropriate action in relation to the collective needs, opportunities and challenges of all South Africans;
- link South Africa with scientific communities at the highest levels, in particular within Africa, and further afield.

VISION

An engine of excellence in scholarship and intellectual cooperation

ASSAf aspires to be the apex organisation for science and scholarship in South Africa, internationally respected and connected, its membership simultaneously the aspiration of the country's most active scholars in all fields of scientific enquiry, and the collective resource making possible the professionally managed generation of evidence-based solutions to national problems.

MISSION STATEMENT

Clarifying the niche of the Academy

Like democratic South Africa in general, ASSAf aspires to play both a national and an international role, particularly with respect to the African continent. We see the Academy as being usefully at arm's length from government and other organised sections of the state, comprising an assembly of excellent scholars from many disciplines who are well networked both nationally and internationally, and have shown their interest in and capacity for promoting the development of a prosperous and fully enabled society. Membership of the Academy (by election) is both an honour and an obligation to work individually and collectively (as the Academy) to ensure that decision-making requiring scholarly scrutiny and analysis is based on the best and most integrated understanding and insights available to the country. The academicians thus represent an organised, independent but responsive scholarly voice to help guide the development of the country and its people.

The mission of ASSAf is thus to:

- become increasingly associated in the mind of the nation with the highest levels of scholarly achievement and excellence in the application of scientific thinking for the benefit of society;
- consolidate its infrastructure and capacity, and to expand and mobilise the membership to ensure that scholars from a full disciplinary spectrum are available for its work, and that these are indeed both thinkers and doers, willing to put significant effort into the Academy's activities;
- embark on a programme of systematic studies of evidence-based issues of national importance, some proposed by government or other sectors, and some identified by the Academy itself;
- develop a sound and robust methodology for constituting consensus study panels, organising their work, including conferences and workshops, and producing authoritative reports that are well-disseminated and have significant impact;

- alternatively, constitute committees to oversee the Academy's work in broad areas of focus, usually expressed by the holding of national forums on particular key issues, leading to forum reports that have a significant impact on policy and practise;
- publish science-focused periodicals, especially a multidisciplinary journal of high quality (the *South African Journal of Science*) and a science magazine that will showcase the best of South African research to a wide national (and international) audience (*Quest – Science for South Africa*); and to promote the development in South Africa of an indigenous system of research journals of internationally recognised quality and usefulness;
- develop productive partnerships with other organisations, especially (but not only) the National Departments of Science and Technology, Education, Health and Agriculture; the National Advisory Council on Innovation; science councils; higher education institutions, etc., with a view to the building of capacity in science and its applications within the National System of Innovation (NSI);
- create new and diversified sources of funding for the sustainable functioning of an independent Academy;
- communicate effectively with the general and specific public, as well as with partners and sponsors;
- develop a plan for the expansion of the activities of ASSAf in partnership with the national science academies of other countries, including contracted partnership with the US National Academies;
- play a significant role in the international science system, particularly in Africa, through organisations such as the InterAcademy Panel (IAP) and the InterAcademy Council (IAC), the Academy of Sciences of the Developing World (TWAS), the International Council on Science (ICSU), as well as the Network of African Science Academies (NASAC), all in the context of the New Partnership for Africa's Development (NEPAD).

MEMBERS

Core asset of the Academy (each styled 'MASSAf')

After nomination by four existing Members (at least two of whom do so from personal knowledge of the candidate), new Members of the Academy are elected in a secret ballot. The normal criterion for election is significant achievement in the advancement or application of science, and, in addition, Members should be persons who can be expected significantly to assist the Academy in achieving its objectives. By October 2006, ASSAf had over 250 Members drawn by self-categorisation from the earth, economic, life, mathematical, physical, social, technological, education and agricultural sciences as well as the humanities.

COUNCIL

Steering Academy activities and taking responsibility

The affairs of the Academy are governed by a Council comprising 12 members, each of whom holds office for four years. This Council is elected by the Members every two years. For the sake of continuity, six Members continue to serve a further term, while six new Members are elected once they have been nominated according to the constitutional mechanism. To provide a better balance of race, gender or disciplinary area, the Council can co-opt additional Members from persons who were nominated for election to the Council.

The office-bearers are the President, two Vice-Presidents, a General Secretary and a Treasurer. Committees can be formed in order to carry out specific functions, but each must be chaired by a Member of the Academy or, preferably, of its Council. Reports drawn up by its committees or ad hoc task groups are approved by the Council before entering the public domain.

INTERNATIONAL CONNECTIONS

Crucial catalyst for Academy-type activities

ASSAf is an active member of the IAP (InterAcademy Panel on International Issues), a growing organisation that embraces the national science academies of over 90 countries. The Academy of Sciences for the Developing World now has an office in Africa based in Nairobi, and the Network of African Science Academies, of which the President of ASSAf is a Vice-President, is also located in that city. ASSAf became an 'intense partner' of the US National Academies (together with the Nigerian and Ugandan Academies of Science) as part of the African Science Academy Development Initiative (ASADI), receiving a substantial five-year grant to build its capacity for generating evidence-based advice for the government and the nation in general.

STRATEGIC PLAN AND POLICY DEVELOPMENT

The way to go

ASSAf has developed a comprehensive strategic plan following a thorough process for identification of its strengths, weaknesses, opportunities and threats. Through its governing Council, the Academy has developed policies and guidelines for its activities. The initiation of the ASADI partnership with the US National Academies prompted the generation, proposal and adoption of the following items:

- Guidelines for proposals of science-based topics in terms of the ASSAf Act;
- Guidelines for proposals of science-based topics (project proposals);
- Guidelines for the appointment of consensus study panels and forum steering committees;
- Policy on conferences;
- Formation of a forum steering Committee on Science for Poverty Alleviation (first example of an ASSAf 'Board');

- Panel for the Consensus Study on Nutritional Influences on Human Immunity, with special reference to clinical tuberculosis and HIV infection (first ASSAf consensus study).

ASSAf's strategic plan and the Academy's policies and guidelines are publicly featured on the ASSAf website at <http://www.assaf.org.za>

RESEARCH PUBLISHING

The core of the quality assurance system for the dissemination of research findings

The Academy of Science of South Africa signed a contract in 2001 with the DST for various activities in connection with the strategic management of research journals published in South Africa. The first component was a comprehensive study of the present and best-possible future role of research journals published in South Africa, now completed through the release of a full report in March 2006, with evidence-based recommendations, and a range of follow-up project integration and implementation strategies.

SAJS

Publishing the *South African Journal of Science*

The *South African Journal of Science* is the leading multidisciplinary research journal in Africa, and features a great diversity of original work by researchers throughout the country and abroad, concentrating on articles that have an appeal that is wider than that of single disciplines. Among the highlights of the volume published in 2005 were articles featuring the research at historically black universities supported by the Royal Society-NRF bilateral programme. The journal appears six times a year, and is accessible online as one of the e-publications managed by Sabinet.

QUEST

Publishing Quest: A quarterly magazine of high quality, presenting science for South Africa

The Academy publishes the national science magazine *Quest: Science for South Africa* which was launched in 2004. *Quest* serves as a platform for communication about scientific research done in South Africa. It strives to showcase South African science in action, and is aimed at the broad scientific community, decision makers, the public, students, and especially the senior grades at secondary schools.



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A. Academy of Science of South Africa (ASSAf) Publications

A. ASSAf Consensus Study Reports

2009

Revitalising Clinical Research in South Africa

Academy of Science of South Africa (ASSAf)

Academy of Science of South Africa

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